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Health Technology Assessment (HTA)

HTA Report

Title	Revascularisation versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)
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Executive Summary

Background

The aim of this health technology assessment (HTA) is to evaluate the safety, effectiveness, cost, cost-effectiveness and budget impact of revascularisation with percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or both (i.e. PCI or CABG) in comparison to optimal medical therapy (OMT) in patients with chronic coronary syndrome (CCS). Ethical, legal, social and organisational issues related to the interventions are also explored.

Methods

Systematic searches were conducted in MEDLINE, Embase, the Cochrane Library, the INAHTA database, and EconLit up to 29 June 2022. Systematic reviews, randomised controlled trials (RCTs) and nonrandomised studies of interventions (NRSI) published after 1 January 2000 were eligible for inclusion. Relevant outcomes included major adverse cardiac events (MACE), all-cause mortality, hospitalisation, subsequent revascularisation, health-related quality of life (HRQoL), stent thrombosis, myocardial infarction (MI), and stroke. Risk of bias was assessed using study design-specific tools, and the overall strength of evidence for important outcomes was assessed using the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) approach. Separate random-effects meta-analyses were conducted for RCTs and NRSIs using R. Heterogeneity was evaluated qualitatively (i.e. forest plots), and quantitatively (i.e. I^2, Chi^2 and Tau^2).

A systematic review of economic studies was undertaken in the same databases. Data were extracted from retrieved cost and cost-effectiveness studies, and the results described narratively. The applicability of the retrieved cost-effectiveness studies to the HTA context was assessed. None of the existing evidence was directly applicable to the Swiss context, thus a de novo Markov model was built.

Clinical evaluation

RCT results

Seven RCTs were included; 3 compared PCI plus OMT with OMT alone, 1 compared CABG plus OMT with OMT alone, 2 compared revascularisation (either PCI plus OMT or CABG plus OMT) with OMT alone, and 1 compared PCI plus OMT, CABG plus OMT and OMT alone. In total, 10,924 patients (range 396 to 5,179) were included. Risk of bias was ‘high’ in 2 trials and of ‘some concern’ in 5 trials.

CABG plus OMT demonstrated significant favourable results across several outcomes: MACE, hospitalisation (9 fewer hospitalisations per 100 patients; high certainty of evidence) and MI (3 fewer MIs per 100 patients; high certainty of evidence). The benefits of CABG plus OMT were only apparent

for all-cause mortality at 120 months follow-up and subsequent revascularisation at 60 months follow-up. The initially favourable HRQoL scores for CABG plus OMT diminished at longer-term follow-up with no additional benefit compared to OMT alone.

PCI plus OMT reported significant favourable results for HRQoL (general and cardiac-specific), anginal frequency and subsequent revascularisation during the short-term (≤ 24 months). Anginal stability at 12 months was not significantly different, and there were no reported clinical benefits above OMT alone for all-cause mortality, hospitalisation, MI and stroke. MACE only favoured PCI plus OMT at 24 months follow-up, whilst 12- and 60-month follow-up were not significant. Subsequent revascularisation favoured PCI plus OMT up to 24 months, but was insignificant at 60 months.

Revascularisation (i.e. PCI or CABG) plus OMT demonstrated significant favourable results for anginal frequency and general HRQoL at 12 months, treatment satisfaction up to 24 months, and subsequent revascularisation at 60 months (17 fewer subsequent revascularisations per 100; moderate certainty of evidence). Hospitalisation due to HF was significantly lower in the comparison group receiving OMT alone. Other outcomes reported no significant differences, or were not reported.

NRSI results

Eight NRSIs were included; 5 compared PCI plus OMT with OMT alone, 2 compared revascularisation plus OMT with OMT alone, and 1 compared PCI plus OMT, CABG plus OMT, and OMT alone. In total 25,803 (range 83 to 9,676) participants were included. Study quality was acceptable in 7 of the studies. For CABG plus OMT, all-cause mortality, subsequent revascularisation and MI were not significantly different compared with OMT alone; no data was available on hospitalisation or stroke. For PCI plus OMT, all-cause mortality was significantly lower (at 120 months), but there were no clear benefits for MACE or subsequent revascularisation, and no differences for hospitalisation or MI. Stent thrombosis and target vessel revascularisation were significantly lower in participants receiving OMT alone. For revascularisation (i.e. PCI or CABG), all-cause mortality and need for subsequent revascularisation were significantly lower in participants receiving revascularisation plus OMT compared to OMT alone at 60 months follow-up. Hospitalisation and MI were not significantly different.

Economic evaluation

The de novo economic evaluation demonstrated unfavourable outcomes (i.e. high incremental cost-effectiveness ratio [ICER] or dominance) for PCI, CABG and revascularisation (i.e. PCI or CABG) under the base case. Economic outcomes improved when baseline event rates were sourced from more targeted population groups, including patient cohorts with chronic kidney disease or left ventricular ejection fraction ≤35%. For all comparisons, the relative effect of revascularisation with

respect to all-cause mortality was a major driver of cost-effectiveness. The cost of inpatient PCI and CABG procedures, as well as the baseline annual mortality transition, were also important parameters.

Under current policy conditions, CABG and PCI procedures for CCS were estimated to be responsible for anticipated costs of Swiss francs (CHF) 59.7 million and CHF146.1 million in 2023, respectively. Considering observed trends in the use of revascularisation procedures over the period 2016 to 2019 (i.e. reducing utilisation of CABG, increasing utilisation of inpatient and outpatient PCI), anticipated CABG costs were projected to decrease to CHF51.2 million by 2027 while anticipated PCI costs were projected to increase to CHF184.3 million. Scenario analyses using alternative data sources and/or assumptions for PCI procedure numbers found costs for PCI ranging from CHF135.9 million to CHF142.3 million in 2023, and CHF114.1 million to CHF156.2 million in 2027.

Ethical, legal, social, organisational evaluation

Ten publications related to ethical, social and organisational issues were identified; none were identified relating to legal considerations. Regarding ethical issues, treating physicians should ensure patients have a comprehensive understanding of the risks associated with PCI compared to OMT alone, so informed consent can be elicited. Social issues identified that cultural distrust of healthcare providers, patients' perception of their illness, and assumptions by healthcare providers based on patients' social characteristics all impact the care a patient received. However, these social issues are based on patient groups in the USA and may not be applicable to the Swiss healthcare system. Shared decision-making between patients and clinicians can ameliorate these challenges.

Conclusions

The RCT evidence demonstrated generally favourable outcomes for the use of CABG plus OMT compared with OMT alone. For PCI plus OMT, the evidence of a benefit was less clear and was largely limited to short-term outcomes (≤ 24 months). The NRSI evidence was more difficult to interpret due to selection bias, residual confounding factors, unknown participant dropout between treatment groups, limited outcome reporting, and results reporting contradictory findings when reported as hazard ratio or risk ratio. As such, the RCT evidence was deemed more reliable, and was used as the basis for the economic evaluation.

The economic evidence demonstrated unfavourable outcomes (i.e. high ICERs or dominance) for all interventions under base case baseline event rate estimates. For all comparisons, the relative effect of revascularisation with respect to all-cause mortality was a major driver of cost-effectiveness. Economic outcomes improved when baseline event rates were sourced from more targeted population groups, including patient cohorts with chronic kidney disease or left ventricular ejection fraction ≤35%.

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Abbreviations and acronyms

ACE inhibitors	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndrome/symptoms
ARBs	Angiotensin receptor blockers
BMS	Bare-metal stent
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCB	Calcium channel blockers
CCS	Chronic coronary syndrome
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss franc
CI	Confidence interval
CMRI	Cardiac magnetic resonance imaging
COPD	Chronic obstructive pulmonary disease
CCTA	Coronary computed tomography angiography
CTO	Chronic total occlusion
CUA	Cost-utility analysis
CVD	Cardiovascular disease
DALY	Disability-Adjusted Life Year
DAPT	Dual antiplatelet therapy
DEB	Drug-eluting balloon
DES	Drug-eluting stent
DRG	Diagnosis-related group
ECG	Electrocardiogram
EQ-5D	European quality of life 5-dimension questionnaire
ESC	European Society of Cardiology
FOPH	Federal Office of Public health
GRADE	Grading of Recommendation, Assessment, Development and Evaluations
HF	Heart failure
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICA	Invasive coronary angiography

ICHOM	International Consortium for Health Outcomes Measurement
IMA	Internal mammary/thoracic artery
INAHTA	International Network of Agencies for Health Technology Assessment
LAD	Left anterior descending artery
LDL-C	Low-density lipoprotein cholesterol
LMCA	Left main coronary artery stenosis
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
MacNew	Quality of life after myocardial infarction questionnaire
mg/dL	Milligrams per decilitre
MI	Myocardial infarction
MIDCAB	Minimally invasive direct coronary artery bypass grafting
mmol/L	Millimoles per litre
NRSI	Nonrandomised study of interventions
N.A.	not applicable
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin-kexin type 9
PICO (EO)	population, intervention, comparator, outcome (economic outcomes)
PET	Positron emission tomography
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality-adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
REV	Revascularisation
RR	Risk ratio
SAQ (-7)	Seattle Angina Questionnaire (-7)
SD	Standard deviation
SF-36	Short form-36
SIHD	Stable ischaemic heart disease
SMD	Standardised mean difference
SoF	Summary of findings
SYNTAX (II)	Synergy between PCI with Taxus and Cardiac Surgery (II)
TECAB	Totally endoscopic coronary artery bypass

TVR	Target vessel revascularisation
VKA	Vitamin K antagonist
WHO	World Health Organization

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytical methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative, systematic and transparent, and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety, cost, cost-effectiveness and budget impact, and ethical, legal, social and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

Each HTA topic entails a policy and a research question. In healthcare, a policy question is a request to regulate a reimbursement policy and is aimed at securing financing of health technologies. Such a request, related to a particular health technology, typically addresses an existing controversy around a technology.

Patients with chronic coronary syndrome (CCS) may be treated with conservative methods including optimal medical therapy (OMT) which consists of a group of medications for managing heart conditions and high blood pressure, lowering cholesterol and thinning the blood to prevent sudden heart attacks and heart failure (HF). Additionally, patients may receive advice on risk factor modifications (lifestyle modifications etc.) with or without invasive interventions.[1-3] Revascularisation is an invasive intervention in which patients undergo percutaneous coronary intervention (PCI)—also known as angioplasty or percutaneous transluminal coronary angioplasty (PTCA)—or coronary artery bypass grafting (CABG).[1] These interventions aim to improve health-related quality of life (HRQoL) and reduce mortality.

Revascularisation procedures have been performed for decades and are well established as standard practice in patients with acute coronary syndromes (ACS).[4-6] However, controversies regarding their implementation in CCS patients remain.[6,7] Regarding mortality in CCS patients, clinical trials have yet to demonstrate which is superior—invasive or conservative intervention.[8-13]

The aim of this HTA is to determine the efficacy/effectiveness, safety, cost, cost-effectiveness and budget impact of PCI plus OMT compared to OMT alone, and CABG plus OMT compared to OMT alone.

2 Research question

To answer a policy question, research questions must be defined and answered first. The **research questions** are answered by inquiry into the HTA topic, which requires data collection and analysis. Research questions are specific and narrow. This HTA report addresses the following research questions:

1. What are the benefits and harms of PCI plus OMT and CABG plus OMT, compared to OMT alone for the treatment of CCS?
2. What are the cost-effectiveness and budget impacts associated with PCI plus OMT and CABG plus OMT, compared to OMT alone for the treatment of CCS?
3. What are the ethical, legal, social and/or organisational issues associated with PCI plus OMT and CABG plus OMT, compared to OMT alone for the treatment of CCS?

3 Medical background

3.1 Pathophysiology, symptoms and prognosis

CCS is also referred to as stable coronary artery disease (CAD), coronary heart disease, ischaemic heart disease and multivessel disease.[14] The signs and symptoms of CCS include ischaemia, angina and atherosclerotic plaque accumulation in coronary arteries. To be classified as CCS and not another form of cardiovascular disease (CVD), the signs and symptoms have to be stable for an extended period of time (typically 12 months post-ACS) and be controllable by pharmaceutical intervention or revascularisation procedures.[1,15] In addition, coronary artery chronic total occlusions (CTOs) are an exacerbation of CCS with advanced calcification.[16]

The pathophysiology of CCS is defined by atherosclerosis of the coronary arteries of the heart.[1,14,17] Plaque accumulation on the inner tissue of the coronary arteries is known as an atherosclerotic lesion.[18] When an atherosclerotic plaque develops in the wall of a coronary artery, the artery undergoes remodelling in which the luminal area of the vessel is enlarged. Atherosclerotic plaques can be stable or unstable; an unstable plaque may rupture, resulting in thrombus formation that may not produce complete occlusion of the artery but causes partial blockage of one of the coronary arteries and reduces the flow of oxygen-rich blood to the heart muscle. This produces unstable angina or a non-ST elevation myocardial infarction (MI).[19] An acute complete occlusion of the artery results in an ST elevation MI (STEMI) and may lead to sudden cardiac death.[18,19] Additionally, protruding plaque may reduce the diameter of the artery and restrict blood flow to the heart muscle (i.e. myocardial ischaemia). The extent of artery narrowing (stenosis) is not necessarily dependant on lesion size because the artery may be enlarged through remodelling processes.[19] Stenoses less than 70% are unlikely to result in symptoms, even during stress testing.[19]

Patients may experience CCS differently. Some may present symptomatically, others asymptomatically.[20] Symptomatic patients report signs and symptoms such as burning pain or pressure of the chest (angina pectoris), shortness of breath, chest discomfort, or a sense of impending doom, which may also cause nausea, faintness and restlessness.[1,14,17,20] Discomfort is most often reported as being in the chest, but may come from the epigastrium, the lower jaw or teeth, between the shoulder blades, or from the arms, wrists or fingers.[1,21] These symptoms may be induced or exacerbated by stress and exercise.[1] Patients with stable angina pectoris experience reversible symptoms that occur reliably and repetitively over months and years.[22]

Risk factors for developing CCS include obesity, smoking, family history of heart disease, hypertension, chronic kidney disease, diabetes mellitus (type 1 and 2) and dyslipidaemia.[1,3,14,17] Without risk factor

modifications or treatment, patients with CCS are at high risk of ACS and death. The goal when treating CCS is to reduce cardiac morbidity, reduce risk of acute cardiac events, and improve quality of life through the management of symptoms. It is recommended that all patients are prescribed medication and adopt lifestyle modifications, with or without undergoing revascularisation.[1,23]

3.2 Diagnosis

Diagnosing CCS uses an extensive stepwise approach that generally involves patient history, physical examination, family history, consideration of comorbidities and quality of life, diagnostic testing and imaging.[1,17] Diagnostic testing for CCS, and possible concurrent cardiac and/or pulmonary conditions, can be non-invasive or invasive. Invasive testing is generally only considered in situations where non-invasive testing produced inconclusive results, or for high-risk patients where the type of revascularisation (i.e. PCI or CABG) to be undertaken can only be determined with detailed visualisation.[1] Common invasive and non-invasive diagnostic testing methods used in Switzerland are detailed below.

3.2.1 Non-invasive testing

- **Biochemical tests:** laboratory investigations that identify cardiovascular risk factors (e.g. high cholesterol, diabetes mellitus type 1 or 2, renal dysfunction) and disease prognosis. Common tests include haemoglobin A1c, lipid profile (e.g. total cholesterol, high density lipoprotein, triglycerides, low-density lipoprotein cholesterol [LDL-C]), troponin T or I (for myocardial injury), and glomerular filtration rate.[17]
- **Electrocardiogram (ECG) – resting or exercise:** records cardiac electrical activity.[17] Resting ECGs are a standard test used on patients with unexplained angina, chest pain and/or chest discomfort. Exercise ECGs are rarely used, but do provide valuable complementary information on exercise tolerance, blood pressure, event risk and arrythmias.[1,17] Risks related to different diagnostic tests need to be weighed against the benefits to the individual. For example, exposure to ionising radiation associated with coronary computed tomography angiography (CCTA) and nuclear perfusion imaging needs to be taken into account, especially in young individuals.[1]
- **Echocardiogram (echo) – resting or stress**: details cardiac structure, function and anatomy using sound waves.[17] Resting echo is a clinical tool to aid in the identification of regional wall motion abnormalities (indication of CCS) and diastolic functions. Decreased left ventricular (LV) function and/or regional wall motion abnormalities may increase the suspicion of ischaemic myocardial damage.[1] Echocardiography can also aid in the diagnosis of concurrent cardiac diseases (HF, valvular diseases, cardiomyopathies etc.). Stress echocardiography with

exercise or dobutamine stress is an accurate technique for the detection of obstructive CAD and risk among patients with suspected CCS.[1,17]

- **Cardiac magnetic resonance imaging (CMRI) – resting or stress**: details cardiac anatomy and function when echo is inconclusive.[17] Resting CMRI can evaluate both regional and global cardiac function. Imaging can also evaluate systolic cardiac function and cardiac anatomy. Late gadolinium enhancement of CMRI supports the characterisation of myocardial tissues. This specialised technique reveals myocardial pathology such as scarring and fibrosis.
- **Chest X-ray:** uses minimal doses of ionising radiation to produce images of the chest cavity.[24] Chest X-ray does not provide information directly important to CCS diagnosis but is helpful in detecting potential HF and/or pulmonary conditions. The main use of chest X-rays is to exclude additional causes of atypical presentation of chest pain.[1]
- **Coronary computed tomography angiography (CCTA):** uses ionising radiation (X-ray imaging) to visualise the heart and the lumen of surrounding arteries.[25] CCTA provides detailed atherosclerotic plaque characterisation and the ability to assess functional significance of specific lesions.[26]
- **Coronary calcium score:** for plaque detection may provide useful information about the atherosclerotic risk in selected patients.[1]
- **Positron emission tomography (PET):** is a combination of biochemical analysis and nuclear medicine that measures the metabolic activity of cells. PET is used to visualise any biochemical changes in the heart or blood vessels. For example, PET can visualise the metabolism of heart muscles.[27]
- **Myocardial perfusion scintigraphy:** is a form of nuclear medicine. The stress test is used to visualise blood flow through heart muscle as well as determine how well the heart muscle is pumping blood throughout the body.[28]

3.2.2 Invasive testing

- **Invasive coronary angiography (ICA):** a catheterisation procedure that uses ionising radiation (rapid X-ray imaging) to visualise the heart and lumen of surrounding arteries. ICA is recommended for risk stratification in conjunction with fractional flow reserve in symptomatic patients with a high-risk clinical profile. In some circumstances, ICA may be indicated if non-invasive testing indicates that a patient is at high risk of a cardiac event and the type of revascularisation (i.e. PCI or CABG) must be determined.[1]

3.3 Epidemiology and burden of disease

CVD is a term that represents a group of diseases affecting the heart and blood vessels (CCS, HF etc.).[29-31] It is a leading cause of death in Switzerland and globally.[29,30] In 2019, CVD was the number one cause of death in Switzerland, responsible for 29% of all deaths.[29] Ischaemic heart disease was the cause of death for 6,785 individuals in 2019. Mortality rates were reported as 54.4 men and 24.9 women per 100,000 inhabitants.[29] In 2015, there were 19,501 reported new cases of CCS in Swiss men and 15,370 new cases in women.[32] Switzerland has one of the lowest rates of age-standardised disability-adjusted life years (DALYs) lost in males due to stroke, ischaemic heart disease and other CVDs.[32] Furthermore, in 2018 a Swiss cohort of CCS patients reported a 0.2% mortality rate after PCI.[33]

Statistics from the United States of America (USA) report that 38% of all deaths are attributable to CVD, and of these, 47% were patients with CCS.[34] In 2015, CCS accounted for approximately 14% of deaths in men and 12% in women in Europe.[32] European men with CCS lost more than 21 million DALYs (14%); European women lost around 14.5 million (11.3%) DALYs.[32]

3.4 Treatment pathway

Treatment for CCS depends on a variety of risk factors including comorbidities (e.g. hypertension, diabetes mellitus type 1 and 2, obesity, hyperlipidaemia, chronic kidney disease), exercise regimen and the presence of symptoms.[1,20,23,35] In general, the first step in a treatment pathway is to assess symptoms and perform clinical investigations. For patients suspected of having unstable angina clinicians will manage them by following the ACS guidelines. Identifying comorbidities and determining the patient's quality of life informs whether revascularisation is feasible, or when it is futile and medical therapy is the appropriate option. Non-invasive testing such as resting ECG, biochemistry, chest X-ray (in selected patients), and echocardiography at rest are used in the diagnostic management. Where patients are found to have a left ventricular ejection fraction (LVEF) <50% the treatment pathway will follow general recommendations for the management of patients with CCS and symptomatic HF due to ischaemic cardiomyopathy and left ventricular systolic dysfunction. Causes of chest pain other than CAD need to be considered and treated as appropriate.[1] The likelihood of obstructive CAD is influenced by the prevalence of the disease in the population, as well as by clinical features of an individual patient. A simple predictive model can be used to estimate the pre-test probability of obstructive CAD based on age, sex and symptoms.[1] Further diagnostic testing may include CCTA. Where obstructive CAD is determined, appropriate therapy is offered based on symptoms and event risk.[1] If a patient is tolerating OMT and does not develop symptoms or the disease does not progress, the patient will continue with CCS management under the treating physician. In contrast, if a patient is not tolerating OMT or disease progresses, the patient will likely be indicated for invasive coronary angiogram.

A patient's synergy between PCI with paclitaxel-eluting taxus stents and cardiac surgery II (SYNTAX II) score, comorbidities and/or additional diagnostic information (***Section 3.2***) may be used to determine if they are indicated for PCI or a CABG procedure.[36] (This tool was developed with the SYNTAX II trial, incorporating the anatomical presentation of the disease to determine complexity and risk of CCS.[36]) After surgery, patients are generally treated with OMT (if tolerated by the patient). In addition, lifestyle modification significantly decreases the risk of future cardiovascular events. These include smoking cessation, recommended physical activity, a healthy diet and maintaining a healthy weight.[1]

4 Technology

Invasive and non-invasive treatments are available for the treatment of symptomatic CCS patients, with several modifications of each therapy to suit individual needs.[1] The 2019 European Society of Cardiology (ESC) guidelines highlight 3 primary goals of CCS treatment:[1]

- improve HRQoL by reducing the frequency and severity of angina pectoris and other somatic and psychological complaints
- reduce CCS-related morbidity (non-fatal MI and HF)
- reduce cardiovascular-related mortality.

4.1 Invasive interventions

PCI and CABG are invasive interventions that aim to restore blood flow in areas of myocardial ischaemia.[1] Clinical characteristics, such as comorbidities (e.g. diabetes mellitus type 1 and 2, chronic kidney disease, chronic obstructive pulmonary disease [COPD], obesity), LVEF, presence of multivessel disease and presence of main stem stenosis, and the SYNTAX II score determine if a patient is indicated for PCI or CABG.[37]

Some patients may have to undergo subsequent invasive revascularisation procedures.[38,39] Compared to PCI-naïve patients, those with a prior PCI are at increased risk of having to undergo CABG within 6 months due to higher risk of ischaemia and multivessel disease.[39] Similarly, patients that underwent a PCI within 6 months of their original PCI are twice as likely to have an additional PCI compared to revascularisation-naïve patients.[39] This is often because several PCI procedures are needed to achieve complete revascularisation. However, patients that had a prior CABG are less likely to have to undergo an additional CABG procedure compared to revascularisation-naïve patients.[39]

4.1.1 Percutaneous coronary intervention

PCI is a minimally invasive approach in which stenoses are directly manipulated to restore patency of vessels and blood flow to the affected myocardial area. This may be performed via the placement of a bare-metal stent (BMS), drug-eluting stent (DES) or balloon or drug-eluting balloon angioplasty.[40-42] The individual procedures are described as follows:

- **Bare-metal stent (BMS) angioplasty:** A catheter moves a stent to the stenosis to mechanically sustain the opening of the artery and plaque.[40] BMS was first implanted into a human coronary artery in 1986.[42] In 2018, 0.2% of stents implanted in Switzerland were BMS.[42]
- **Drug-eluting stent (DES) angioplasty:** DES is the most common stent choice in angioplasty.[33] DES stents act similarly to BMS, but are coated with medications to prevent restenosis through

neointimal hyperplasia.[40] Three generations of DES have been utilised since the first implantation in 1999.[41,42] In 2018, 99% of the stents implanted in Switzerland were DES.[33]

- **Balloon angioplasty:** A catheter device moves the deflated balloon through a leg or arm artery to the location of the stenosis. The balloon is inflated, thus dilating the artery and dissecting the plaque.[40,42] Afterwards, the device is retracted and removed.[40,42] Balloon angioplasty was first used to treat CCS in 1977.[41,42] According to clinical experts, this procedure is rarely performed and is generally reserved for smaller vessels.
- **Drug-eluting balloon (DEB) angioplasty:** This procedure and technology is similar to a traditional balloon angioplasty (described above).[43,44] In this procedure the balloons are used to deliver a homogenous coating of antiproliferative agents (immediate-release high-concentration short-acting pharmaceuticals) to the surface of lesions.[43,45] DEBs are designed to compress the plaque while concurrently eluting pharmaceuticals that prevent restenosis (growth of vascular smooth muscle tissue) of the artery.[43-45] Unlike DES and BMS, DEB can be utilised in tortuous (i.e. long complex, twisted) vessels, small vessels and calcified vessels.[43]

Restenosis is a common adverse event of PCI, occurring in less than 5% of patients within 1 year of DES placement.[42 46,47] Strut thickness of the stent is key in reducing restenosis.[48] DESs coated with medications that inhibit cell proliferation and activate signal transduction pathways chemically prevent restenosis, whereas the other 2 technologies offer drug-free treatment.[40-42,49] The challenge of restenosis (and accompanying chronic inflammation) is decreased in DEB compared to DES, as no stent polymer or scaffolding is implanted into the arterial wall.[44,45] After delivery of the pharmaceutical and plaque compression by the balloon, the artery can resume its original shape with minimal disturbance, diminishing the possibility of abnormal arterial flow.[45]

4.1.2 Coronary artery bypass grafting

CABG is used to bypass stenoses using veins or artery conduits grafted from elsewhere in the body (e.g. legs and arms).[50,51] The procedure generally involves access to the heart by a full sternotomy (division of the sternum).[52] Various techniques can be used to conduct the CABG procedure, including use of a cardiopulmonary bypass machine or performing minimally invasive surgery.[52,53]

4.1.2.1 Types of grafts

The bypass graft may be a complete graft (artery or vein) or a partial graft (artery/vein mix). Conduits used as grafts are generally harvested from a saphenous vein, radial artery or internal mammary/thoracic artery (IMA).[14,50,51,54] Saphenous vein grafts are often used because the conduits can easily be harvested from a patient's legs. The superiority of either graft will not be addressed in this HTA as it is beyond the scope of the research questions (***Section 6***).

4.1.2.2 Cardiopulmonary bypass machine

CABG may be performed with or without the use of a cardiopulmonary bypass machine (i.e. on-pump vs off-pump).[52,55] The machine provides the option of a bloodless surgical field as it can artificially circulate oxygenated blood through the patient's body after the heart has been stopped (i.e. cardioplegic arrest).[52,55] In contrast, the heart is not stopped during an off-pump CABG procedure,[52,56] instead other stabilisation techniques are used and the necessary coronary anastomoses are performed on the beating heart.[52,55,56] Typically, a CABG procedure is performed on-pump unless deemed unsafe due to the patient's clinical presentation (e.g. calcification of the aorta that prevents aortic clamping).[52,57,58] Cardiopulmonary bypass has been previously associated with an increased risk of post-surgery morbidity in patients with comorbidities (e.g. diabetes mellitus type 1 and 2, chronic kidney disease, COPD, obesity).[52,59] Off-pump CABG is a newer technique with the proposed benefit of lower complication rates.[60]

4.1.2.3 Minimally invasive direct coronary artery bypass grafting

Minimally invasive CABG procedures (referred to as a minimally invasive direct coronary artery bypass grafting [MIDCAB]) are performed infrequently and generally reserved for CCS patients that have complex lesions and/or stenoses (both single-vessel and multivessel) in the left anterior descending artery (LAD), for whom treatment with PCI or standard CABG is deemed too risky.[53,59,61] Unlike standard CABG, the procedure avoids a full sternotomy and use of the cardiovascular bypass machine.[59,61] During the procedure, the LAD is accessed via a 5–6-cm incision in the fourth or fifth left intercostal space.[59] The graft is harvested from the left IMA at the level of the first rib.[59] Anastomosis of the conduit grafted from the IMA to a stabilised LAD is performed on a beating heart.[59,61]

4.2 Non-invasive treatment

4.2.1 Optimal medical therapy

OMT (also known as pharmacological management) is a systemic conservative form of CCS treatment, in which pharmaceuticals are used alongside invasive coronary surgery.[1] OMT can also be used as a standalone treatment.[1,23] It is recommended that patients are monitored for 2–4 weeks after commencement of OMT to review response to therapy.[1] There is no universally accepted treatment regimen of OMT for CCS patients because the prescribed therapy is patient-specific and based on intolerances, contraindications and comorbidities.[1,23,62] The 2019 ESC guidelines determine how OMT is prescribed to CCS patients in Switzerland. OMT detailed in these guidelines is described below and will be used as the standard definition of OMT described in the population, intervention, comparator, outcome (PICO) criteria (***Section 5***).[1]

ESC recommends a variety of drug class combinations for CCS patients to manage symptoms, slow disease progression and/or prevent acute events.[1] These include antiplatelet therapy, anti-ischaemic/antianginal therapy, renin angiotensin system blockers and lipid-lowering therapy.[1]

The drugs and applications recommended by the ESC to treat CCS patients are detailed below.[1]

- **Antiplatelet therapy:** prevents blood clot formation by stopping platelets sticking together. Dual antiplatelet therapy (DAPT) with aspirin and an oral P2Y12 inhibitor is the mainstay of antithrombotic therapy after MI and/or PCI. Aspirin should normally be continued in patients with CCS undergoing elective cardiac surgery, and other antithrombotic drugs stopped at intervals according to their duration of action and indication.[1]
    - **Aspirin:** is the most commonly prescribed antiplatelet therapy. The drug inhibits the cyclooxygenase activity within the prostaglandin synthesis pathway.[63]
    - **Oral P2Y12 inhibitors:** prasugrel and ticagrelor are antiplatelet therapies. Prasugrel is indicated for patients who have experienced acute coronary events such as MI who have tolerated DAPT for 1 year and post-PCI. Clopidogrel and ticagrelor are indicated in post MI patients who have tolerated DAPT for 1 year.[64]
- **Anti-ischaemic/antianginal therapy:** relieves angina and ischaemic symptoms, but does not prevent cardiovascular events in most patients.[1]
    - **Beta-blockers**: are used for angina and ischaemia relief in most patients with CCS. Beta-blockers are the first-line choice in patients with CCS.[1] In patients with left ventricular dysfunction, HF or previous STEMI beta-blockers showed significant reduction in mortality and/or cardiovascular events.[1]
    - **Calcium channel blockers (CCB)**: antianginal therapy for the relief of ischaemia or angina and to control heart rate. Verapamil and diltiazem are typically used in Switzerland to treat CCS. On occasion, amlodipine is also used in Switzerland.[1,2,65] There are 2 sub-classes of CCB:
        - **Non-dihydropyridine CCBs:** reduce heart rate due to high myocardial selectivity. Popular non-dihydropyridine CCBs include verapamil and diltiazem.[66,67]
        - **Dihydropyridine CCBs:** reduce blood pressure due to high vascular selectivity. A first-line therapy in patients presenting with low resting heart rate. These may be effective for treatment of angina where symptoms are unresolved with beta-blockers or CCB. Examples of dihydropyridine CCBs include nifedipine and amlodipine.[2]
    - **Nitrates**: Short-acting nitrates (e.g. sublingual and spray nitroglycerin) are available for immediate relief of angina symptoms. Long-acting nitrates (e.g. nitroglycerin, isosorbide)

are prescribed as a second-line treatment when dihydropyridine CCBs are contraindicated, not well tolerated by patients and/or provide no symptom relief.[1]

- **Renin angiotensin system blockers:** relaxes veins and arteries to lower blood pressure and make it easier for the heart to pump blood.
    - **Angiotensin-converting enzyme (ACE) inhibitors**: relaxes veins in high-risk patients. These are primarily prescribed for individuals with concurrent hypertension, LVEF ≤ 40%, diabetes mellitus (type 1 and 2) or chronic kidney disease.
    - **Angiotensin receptor blockers (ARBs):** substitute for patients intolerant to ACE inhibitors. It should be noted that combining ARBs and ACE inhibitors may lead to an increase in renal adverse events in hypertension patients, so this is not recommended.
- **Lipid-lowering therapy:** reduces cholesterol.
    - **Statins:** block the enzyme the liver uses to produce cholesterol. Common statins include atorvastatin, rosuvastatin, simvastatin, fluvastatin, pitavastatin and pravastatin.[2] The goal of treatment is to lower LDL-C by at least 50% from baseline to <1.4 mmol/L (<55 mg/dL). In patients who have experienced a second event within 2 years, a lower target may be set.[1]
    - **Ezetimibe:** reduces the amount of cholesterol absorbed through a patient's diet.[68] This drug may be taken in combination for patients who are unable to reach their LDL-C goals.[1]
    - **Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors:** lipid-lowering drugs (e.g. evolocumab, alirocumab) that can reduce LDL-C by binding to LDL receptors and causing lysosomal degradation.[69] These drugs are generally prescribed to patients who fail to meet LDL-C targets using statins and/or ezetimibe.

Clinical experts have advised that OMT regimens differ before and after revascularisation. Patients who have undergone revascularisation are likely to be on DAPT and are likely to require less antianginal medication; this can be for up to 12 months with PCI. Conversely, patients treated with OMT alone may require more antianginal therapy and fewer antiplatelet drugs. A small study in a Swiss CCS population in 2008 found almost all patients with CCS were prescribed antiplatelet therapy (98.6%).[70] Statins (84%), beta-blockers (75%), calcium antagonists (34%) and nitrates (51%) were also commonly administered.[70]

It is important that lifestyle changes are made alongside OMT. Lifestyle changes (e.g. weight management, healthy diet, smoking cessation and regular physical activity) are a vital part of CCS treatment.[1,23] However, they will not be considered in this HTA as it is beyond the scope of the research questions (***Section 2***).

5 Population, Intervention, Comparator, Outcome (PICO)

Table 1 PICO criteria

Population	Adults diagnosed with symptomatic CCS [a] *Exclusion criteria: ACS-naïve patients with no symptoms of CCS; ACS patients; patients that experienced MI or unstable angina in the past 12 months*
Intervention	Invasive procedure(s) + OMT: 1) CABG + OMT 2) PCI + OMT, including: a. Angioplasty with DES + OMT [b] b. DEB angioplasty + OMT 3) CABG or PCI + OMT [c] *Exclusion criteria: CABG with concurrent PCI*
Comparator	OMT administered to reduce the risk of cardiac events and relieve symptoms (angina and ischaemia) [d]
Outcomes	**Clinical outcomes** [e] • MACE [f] – composite of all-cause mortality, MI [g], subsequent revascularisation, hospitalisation (i.e. MI, stroke [ischaemic, haemorrhagic], HF) [g] or stroke • All-cause mortality • Hospitalisation (i.e. MI, stroke [ischaemic, haemorrhagic], HF) [g,h] • Subsequent revascularisation • HRQoL • General HRQoL measures (e.g. SF-36, EQ-5D, etc.) • Cardiac-specific HRQoL (e.g. SAQ-7, etc.) • Stent thrombosis [g,i] • MI • Stroke • Hospitalisation due to HF • Target vessel revascularisation **Health economic outcomes** • Budget impact • Cost-effectiveness/cost-utility • Direct medical costs of the technology and associated services

Abbreviations:

ACS: acute coronary syndrome; **CABG**: coronary artery bypass graft; **CCS**: chronic coronary syndrome; **DEB:** drug-eluting balloon; **DES:** drug-eluting stent; **HF:** heart failure; **HRQoL:** health-related quality of life; **MACE**: major adverse cardiac events; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **SAQ-7**: Seattle Angina Questionnaire; **SF-36**: short-form 36; **TVR:** target vessel revascularisation.

Notes:

[a] Signs and symptoms include ischaemia, angina, angina with concurrent shortness of breath, atherosclerotic plaque accumulation in coronary arteries, and/or 100% occlusion of a coronary artery for a minimum of 3 months (chronic total occlusion).[1,15,16]

[b] Deviation from the study selection criteria predefined in the HTA protocol (***Table 1***). The generation of DES could not be determined in the majority of the included trials. Furthermore, the decision to limit inclusion to the third generation DES was informed by a single clinical reviewer during the protocol phase of the HTA.

[c] Deviation from the study selection criteria predefined in the HTA protocol (***Table 1***). The ISCHEMIA trial appears to only publish the results of revascularisation (CABG & PCI) and OMT compared to OMT. During the protocol review phase the clinical reviewers highlighted the importance of the ISCHEMIA trial in informing current clinical practice. Therefore, the study selection criteria were adjusted at the HTA phase to include trials that combine CABG & PCI.

[d] OMT regimens are patient-specific and account for drug intolerances, comorbidities and non-adherence issues. As OMT is administered in both trial arms, the specifics of the OMT are considered negligible, thus any OMT regimen will be accepted. If details are available,

these will be evaluated against the European guidelines on chronic coronary syndromes,[1] excluding studies that are not applicable to the Swiss healthcare system (e.g. use of novel drugs or inappropriate drug combinations).

[e] Deviation from the study selection criteria predefined in the HTA protocol (***Table 1***). Total adverse events and serious adverse events were removed as clinical outcomes during the HTA phase as included trials defined the respective outcomes events differently and it was impossible to standardise them.

[f] Individual components of MACE (i.e. MI, stroke, revascularisation [limited to TVR], all-cause mortality and hospitalisation [limited HF]) were analysed separately to inform the cost-effectiveness analysis.

[g] Deviation from the study selection criteria predefined in the HTA protocol (***Table 1***).

[h] Eligible new hospital admissions for patients with coronary heart disease were limited to the International Consortium for Health Outcomes Measurement (ICHOM) definition.[71]

[i] Stent thrombosis has been included to capture a major safety concern associated with PCI.

5.1 Population

The population of interest includes adult patients with symptomatic CCS (including CTO). Patients have CCS when they are diagnosed with atherosclerotic coronary arteries without acute symptoms and have not experienced an acute event in the past 12 months.[1] Acute events include, but are not limited to, MI and unstable angina.[1,72] CCS patients considered at high risk of having an acute event (e.g. those with comorbidities, multivessel disease or left main coronary artery disease) were included. Similarly, patients that have previously undergone revascularisation procedures will be included. ACS-naïve patients (i.e. reduced oxygen supply to the heart) with no symptoms of CCS were excluded, because they are generally ineligible for PCI or CABG. [20,35] In addition, no limitations were placed on how long a patient has been symptomatic.

5.2 Intervention

The intervention of interest is coronary artery revascularisation (CABG or PCI) with concurrent OMT. The PCI techniques were limited to angioplasty (including DEB only) with or without stenting. Initially, only third generation DES were considered for inclusion. However, due to publications not providing information on the type of DES utilised in trials, the inclusion criteria were expanded to include all generations of DES. CABG included procedures performed with and without a cardiopulmonary bypass machine (i.e. off-pump vs on-pump) as well as procedures that are 'open' and minimally invasive (i.e. MIDCAB and totally endoscopic coronary artery bypass [TECAB] surgery). No limitations were placed on composition of the CABG graft (i.e. complete [arterial] graft or partial [arterial/vein] graft) or from where the CABG graft was harvested (mammary, saphenous etc.). Studies that included CABG with concurrent PCI were excluded.

5.3 Comparator

The relevant comparator is OMT. Because OMT regimens are idiosyncratic, there is no universal definition.[1,62] OMT can be defined as the treatment that satisfactorily controls symptoms and prevents cardiac events associated with CCS with maximal patient adherence and minimal adverse events.[1] This

typically includes anti-anginal and anti-ischaemic medication. However, a limitation will be placed on OMT to ensure that the treatment in the included studies is consistent with the 2019 ESC recommendations.[1] This will ensure that the OMT is applicable to the Swiss healthcare context.

5.4 Clinical outcomes

The main aim of treating adult patients with CCS is to relieve angina symptoms, improve quality of life, and reduce mortality and cardiac morbidity (i.e. MI and low LVEF).[1,20,73] Therefore, only clinically important clinical outcomes were included in this HTA. Most of the clinically important outcomes have been defined according to the standardised outcome measurements for patients with CCS, as published by the International Consortium for Health Outcomes Measurement (ICHOM).[71] Additional clinical outcomes (i.e. MI, stroke, hospitalisation due to HF and target vessel revascularisation [TVR]) were incorporated after the finalisation of the HTA protocol, as their inclusion was necessary to inform the cost-effectiveness analysis. Similarly, stent thrombosis was incorporated after the finalisation of the HTA protocol as it provided information on a potentially fatal safety concern associated with PCI.

Major adverse cardiac event (MACE) is a composite endpoint routinely used to evaluate clinical outcomes of cardiovascular interventions.[74-76] There is no clear definition of MACE because the composition and relatedness of the included outcomes differ between settings and study designs.[76] These varying compositions often make it difficult to compare MACE between studies.[76] For the purposes of this HTA, MACE included all-cause mortality, MI, revascularisation, hospitalisation and stroke. Clinical experts have suggested these components are commonly used to define MACE within the Swiss healthcare context. Additionally, MI, stroke, hospitalisation due to HF, and TVR (components of MACE) were included and analysed separately to inform the cost-effectiveness analysis.

All-cause mortality was used to determine if invasive coronary artery surgery (CABG or PCI) with concurrent OMT can be fatal to patients with CCS. Disease-specific mortality (e.g. cardiovascular mortality) has not been included as an outcome because it provides less meaningful information than all-cause mortality in patients with CCS.[1]

Health-related quality of life (HRQoL) can provide patient-centred information on physical, social, emotional and mental health to guide clinical practice.[71,77] The tools used to quantify and gather patient-centred information can be disease-specific or generic.[71,77] Examples of disease-specific HRQoL outcomes that measure cardiac-related symptoms (e.g. chest pain and shortness of breath) include, but are not limited to, the Seattle Angina Questionnaire (SAQ-7), which yields 5 subscale scores: physical limitation, angina stability (whether angina changes in frequency when a patient performs their most strenuous level of activity), angina frequency (frequency of angina over the previous 4 weeks), treatment satisfaction and disease perception; and the Quality of Life after Myocardial Infarction (MacNew)

questionnaire.[71] Examples of tools that measure general HRQoL include the European quality of life 5-dimension questionnaire (EQ-5D) and the 36-item short form health survey (SF-36).[78] No limitations were placed on the type of HRQoL tools included.

Stent thrombosis occurs in CCS patients that have undergone PCI. The condition is a rare and major complication associated with high rates of patient morbidity and mortality.[79,80] Stent thrombosis was included to capture a major safety concern associated with PCI.

Hospitalisation is a common indicator of disease progression.[71] Hospitalisation was used to provide an objective measure of the severity of disease impact on patients. Hospitalisation was limited to MI, stroke (haemorrhagic and ischaemic) and HF.[71] Hospitalisation due to HF was included and analysed separately to inform the cost-effectiveness analysis.

Subsequent coronary artery revascularisation can occur in CCS patients that have previously undergone coronary artery surgery (CABG or PCI).[71] TVR is a component of subsequent coronary artery revascularisation that details if the same artery has had to undergo a revascularisation procedure. TVR was included and analysed separately to inform the cost-effectiveness analysis.

6 HTA key questions

1. Are PCI plus OMT and CABG plus OMT efficacious, effective and safe compared to OMT alone for treatment of CCS?
2. What are the costs associated with PCI plus OMT and CABG plus OMT for the treatment of CCS?
3. Are PCI plus OMT and CABG plus OMT cost-effective compared to OMT alone for treatment of CCS?
4. What is the budget impact of PCI plus OMT and CABG plus OMT for the treatment of CCS?
5. Are there any ethical, legal or social issues associated with PCI plus OMT and CABG plus OMT for the treatment of CCS?
6. Are there any organisational issues associated with PCI plus OMT and CABG plus OMT for the treatment of CCS?

6.1 Additional questions

1. Are the safety and effectiveness of PCI plus OMT and CABG plus OMT compared to OMT alone for treatment of CCS affected by characteristics impacting patient risk? These subgroups include:
    a) comorbidities that classify CCS patients as high risk (i.e. cardiovascular comorbidities including hypertension, valvular heart disease and heart transplantation; non-cardiovascular comorbidities including cancer, diabetes mellitus type 1 and 2, obesity, chronic kidney disease, old age)
    b) male or female sex
    c) refractory angina
    d) left main coronary artery (LMCA) stenosis >50%
    e) LVEF ≤40%
2. Are the safety and effectiveness of PCI plus OMT and CABG plus OMT compared to OMT alone for treatment of CCS affected by prior revascularisation with either PCI or CABG?

7 Effectiveness, efficacy and safety

Summary statement: efficacy, effectiveness and safety

RCT findings: Seven randomised controlled trials (RCTs) were included. Three trials compared PCI plus OMT with OMT alone, 1 trial compared CABG plus OMT with OMT alone, 2 trials compared revascularisation (either PCI plus OMT or CABG plus OMT) with OMT alone, and 1 trial used a three-arm comparison (PCI plus OMT vs CABG plus OMT vs OMT alone). MACE was significantly lower for CABG plus OMT compared to OMT alone. PCI plus OMT was not significantly different for MACE compared to OMT alone at 12 and 60 months follow-up, although 24-month follow-up significantly favoured PCI plus OMT. No significant differences in MACE events were observed between revascularisation plus OMT and OMT alone. All-cause mortality at 60 months was not significantly different between CABG plus OMT compared to OMT alone, but 120-month data significantly favoured CABG plus OMT. No significant differences were found in all-cause mortality for the comparisons PCI plus OMT vs OMT alone or revascularisation plus OMT vs OMT alone. Hospitalisation rates were significantly lower for CABG plus OMT compared to OMT alone at 60 and 120 months follow-up, with a high certainty of evidence. No significant difference was found in hospitalisation rates for the comparisons PCI plus OMT vs OMT alone or revascularisation plus OMT vs OMT alone. Hospitalisation due to HF was significantly lower for CABG plus OMT compared to OMT alone. In participants receiving revascularisation plus OMT, hospitalisation due to HF was significantly lower in the comparison group receiving OMT alone. However, in participants with concomitant chronic kidney disease, no significant differences were found in hospitalisations due to HF. MI was significantly lower for CABG plus OMT compared to OMT alone, with a high certainty of evidence. No significant difference was found in MI, with a high certainty of evidence, for the comparisons PCI plus OMT vs OMT alone or revascularisation plus OMT vs OMT alone. No significant differences were found in the occurrence of stroke for all RCT comparison groups.

NRSI findings: Eight studies were included. Six studies used a retrospective study design and 2 used a prospective study design. Five studies compared PCI plus OMT with OMT alone, 2 studies compared revascularisation plus OMT with OMT alone, and 1 study included three intervention arms (PCI plus OMT vs CABG plus OMT vs OMT alone). MACE at 12 months favoured PCI plus OMT, but longer follow-up data at 60 and 120 months were not significantly different compared to OMT alone in the risk ratio (RR) analysis; in contrast, the hazard ratio (HR) analysis at 60 months found a significant reduction in MACE favouring PCI plus OMT; MACE was not reported for CABG or revascularisation. In one study, all-cause mortality (HR at 60 months) was not significantly different between CABG plus OMT and OMT

alone. All-cause mortality risk (RR analysis) at 60 months for PCI plus OMT was not significantly different compared to OMT alone. One small study (n = 83) reporting data at 120 months reported all-cause mortality risk (RR analysis) to be significantly lower in the PCI plus OMT group compared to OMT alone. However, contradictory results were found for HR analyses where all-cause mortality was significantly lower in PCI plus OMT compared to OMT alone at 60 months. For participants receiving revascularisation plus OMT, all-cause mortality (RR analysis) was significantly lower compared to OMT alone at 60 months. HR analyses supported this finding at 12 months follow-up, but data at 60 months were not significantly different. Hospitalisation rates were not significantly different for PCI plus OMT or revascularisation plus OMT compared to OMT alone, and were not reported for CABG plus OMT. MI was not significantly different for any of the reported comparisons.

7.1 Methodology: effectiveness, efficacy and safety

The proposed methods were developed with reference to the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)*[81] and are presented in accordance with the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[82]

7.1.1 Databases and search strategy

Systematic literature searches were conducted in 5 biomedical databases – PubMed (MEDLINE), Embase (Ovid), the Cochrane Library, the INAHTA database and EconLit up to 29 June 2022. Search strings are presented in ***Appendix A***. Search filters to exclude non-human studies and specific publication types (i.e. editorials, letters to the editor, news articles, conference abstracts) were utilised in all searches. The searches were designed to capture publications in English, French, German and Italian. Grey literature searches were limited to HTA and specialist cardiology websites (***Table 60*** in ***Appendix A***). The clinical trials databases ClinicalTrials.gov, EU Clinical Trials register and the Australian New Zealand Clinical Trials Registry (ANZCTR) (***Appendix A***) were searched to identify relevant unpublished and/or ongoing clinical trials. Search strategies for clinical trial registers are listed in ***Appendix A***. The HTA protocol originally stated that the International Clinical Trials Registry Platform would be searched to identify unpublished or ongoing clinical trials; however, the registry's interference was underperforming, so the 3 aforementioned registries were searched instead.

Given the constant development in PCI and CABG, the searches were limited to include studies published after 1 January 2000. This date was selected because this is around the time that the current era of PCI and CABG started.[41,42,50,53,58,83,84] This date range was endorsed by a Swiss clinical expert. Trials published before this date included PCI and CABG protocols not representative of technology, techniques and populations currently used in contemporary clinical practice in Switzerland.

7.1.2 Study selection

All results from systematic literature searches were imported into Rayyan (Rayyan Systems Inc, USA) for study selection.[85] Rayyan allows for blinded title and abstract screening of citations among independent reviewers and resolution of study inclusion conflicts.[85] Screening was performed to include studies meeting the predefined study selection criteria (***Table 2***). Only studies published in World Health Organization (WHO) Mortality Stratum A countries were included.[86] This limitation ensured that all included studies have a comparable disease burden and cause of death to Switzerland.[86] Exclusion criteria were based on publication type (e.g. case notes, case reports, opinion pieces).

Table 2 Study selection criteria

	Inclusion criteria	Exclusion criteria
Population	Adults diagnosed with symptomatic CCS [a]	ACS-naïve patients with no symptoms of CCS; ACS patients; patients that experienced MI or unstable angina in the past 12 months

Intervention	Invasive procedure(s) with OMT for the treatment of CCS:
	• CABG + OMT
	• PCI + OMT, including:
	  ○ Angioplasty with DES + OMT [b]
	  ○ DEB angioplasty + OMT
	• CABG or PCT +OMT [c]
		• Balloon angioplasty
		• BMS
		• CABG with concurrent PCI

Comparator	Any OMT administered to reduce the risk of cardiac events and relieve symptoms (angina and ischaemia) [c]	

Outcomes	**Clinical outcomes – informed clinical effectiveness** [e]
	• MACE [f] – composite of all-cause mortality, MI [g], secondary revascularisation, hospitalisation (i.e. MI, stroke [ischaemic, haemorrhagic], HF) or stroke [g]
	• All-cause mortality
	• Hospitalisation (i.e. MI, stroke [ischaemic, haemorrhagic], HF) [g,h]
	• Subsequent revascularisation
	• HRQoL
	  • General HRQoL measures (e.g. SF-36)
	  • Cardiac-specific HRQoL (e.g. SAQ-7)
	• Stent thrombosis [g, I]
	• MI
	• Stroke
	• Hospitalisation due to HF
	• Target vessel revascularisation
	Health economic outcomes
	• Budget impact
	• Cost-effectiveness/cost-utility
	• Direct medical costs of the technology and associated services
		Inadequate data (no measures of variance, incongruous data reported between figures and text etc)

	Inclusion criteria	Exclusion criteria
Design/ publication type	**Clinical evidence** • Systematic reviews and meta-analyses • Randomised controlled trials • Non-randomised studies of interventions **Economic evidence** • Cost-effectiveness/utility analyses • Budget impact analyses • Cost analyses	• Single-arm studies • Case reports • Conference abstracts • Letters to the editor • Expert opinions • Editorials • Narrative review articles
Language	English, German, Italian, French	
Country	**WHO Mortality Stratum A countries:**[87] Andorra, Australia, Belgium, Brunei, Canada, Croatia, Cuba, Cyprus, Czech Republic [Czechia], Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Luxembourg, Malta, Monaco, The Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovenia, Spain, Sweden, Switzerland, United Kingdom [UK], and United States of America [USA]	
Date	Studies published on or after 1 January 2000	

Abbreviations:

ACS: acute coronary syndrome/symptoms; **CABG**: coronary artery bypass graft; **CCS**: chronic coronary syndrome; **DEB**: drug eluting balloon; **DES**: drug eluting stent; **HRQoL**: health-related quality of life; **MACE**: major adverse cardiac events; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **SAQ-7**: Seattle angina questionnaire; **SF-36**: short-form 36; **WHO**: World Health Organization.

Notes:

[a] Signs and symptoms include ischaemia, angina, angina with concurrent shortness of breath, atherosclerotic plaque accumulation in coronary arteries, and/ or 100% occlusion of a coronary artery for a minimum of 3 months (chronic total occlusion).[1,15,16]

[b] Deviation from the study selection criteria predefined in the HTA protocol (***Table 1***). The generation of DES could not be determined in the majority of the included trials. Furthermore, the decision to limit inclusion to third generation DES was informed by a single clinical reviewer during the protocol phase of the HTA.

[c] Deviation from the study selection criteria predefined in the HTA protocol (***Table 1***). The ISCHEMIA trial appears to only publish the results of revascularisation (CABG & PCI) and OMT compared to OMT. During the protocol review phase the clinical reviewers highlighted the importance of the ISCHEMIA trial in informing current clinical practice. Therefore, the study selection criteria were adjusted at the HTA phase to include trials that combine CABG & PCI.

[d] OMT regimens are patient-specific and account for drug intolerances, comorbidities and non-adherence issues. As OMT is administered in both trial arms, the specifics of the OMT are considered negligible; thus, any OMT regimen will be accepted. If details are available, these will be evaluated against the European guidelines on chronic coronary syndromes.[1] Excluding studies not applicable to the Swiss healthcare system (e.g. use of novel drugs or inappropriate drug combinations).

[e] Deviation from the study selection criteria predefined in the HTA protocol (***Table 1***). Total adverse events and serious adverse events were removed as clinical outcomes during the HTA phase as included trials defined the respective outcomes events differently and it was not possible to standardise them.

[f] Individual components of MACE (i.e. MI, stroke, revascularisation [limited to TVR], all-cause mortality and hospitalisation [limited HF]) were analysed separately to inform the cost-effectiveness analysis.

[g] Deviation from the study selection criteria predefined in the HTA protocol (***Table 1***).

[h] Eligible new hospital admission for patients with coronary heart disease were limited to the International Consortium for Health Outcomes Measurement (ICHOM) definition.[71]

[i] Stent thrombosis has been included to capture a major safety concern associated with PCI.

Database searches were conducted up to 29 June 2022. As per the method described in the HTA protocol, search results were screened by title and abstract against the study selection criteria by 2 reviewers. To ensure that the inclusion criteria were interpreted consistently by the reviewers, separate training samples were used to establish inter-rater reliability. In each training sample, both reviewers

applied the selection criteria in duplicate to the same batch of publications and compared their selections. Conflicts were resolved through discussion; a third reviewer was not needed. After each randomly selected training sample, inter-rater reliability was measured by calculating Cohen's Kappa score, with a score of 0.7 representing substantial agreement between reviewers. In total, a single sample (k = 250 articles) was used to establish a very high degree of inter-rater reliability (Cohen's Kappa = 0.913).[88,89] After sufficient inter-rater reliability was established, the remaining samples of articles were split between the reviewers and selected independently.

The full text study selection was conducted by 3 reviewers separately. Each full text was checked by a different reviewer during the data extraction phase of the HTA. If consensus could not be reached between the 2 reviewers at this phase, the third reviewer was consulted to assess the full text. Inclusion and exclusion decisions are detailed in a PRISMA flow chart (***Figure 1***).[82] A list of studies excluded by full-text review are detailed in ***Appendix C***.

Study design

Different types of study designs were considered for inclusion. Contemporary systematic reviews and meta-analyses meeting the PICO criteria (***Table 1***) were eligible for inclusion; however, no systematic reviews or meta-analyses met the predetermined PICO criteria (***Table 1***). RCT evidence was included in the absence of, or to update, existing systematic reviews and meta-analyses. Nonrandomised studies of interventions (NRSI) that met the PICO criteria (***Table 1***) were included.

7.1.3 Data extraction

Data were extracted (study-arm level) from included publications by a single reviewer using a standardised template. Data checking was performed against the original publication by a second reviewer. Conflicts between reviewers were resolved by consensus. If consensus could not be reached, a third independent reviewer was consulted. Data extracted included:

- **Study information:** author, country, publication date, randomisation technique (RCTs only), study identifier, enrolment dates, setting (e.g. secondary or tertiary hospital), number of centres, study design, follow-up duration, inclusion and exclusion criteria.
- **Demographic information:** number of participants, age, sex, body mass index, definition of disease, prior acute events, prior revascularisation, comorbidities (diabetes mellitus type 1 and 2, chronic kidney disease, hypertension), LDL-C goals, number of major vessels operated on, time since previous ACS.
- **Intervention and comparator:** PCI (e.g. balloon only, type of stent, number of stents placed), CABG details (e.g. off-pump procedure, on-pump procedure, invasive or minimally invasive), OMT regimen (e.g. medications administered, medication variations).

- **Outcomes of interest:** number of events, final or change-from-baseline scores with standard deviations in any HRQoL measure. Data tables of extracted outcome data are presented in ***Appendix B***.
- **Additional noteworthy factors:** possible effect modifiers (e.g. type of PCI), limitations or key differences of the study.

Where data are presented in a graphical format instead of numerically, the data were estimated using WebPlotDigitizer.[90]

7.1.4 Analysis of study quality

Different appraisal criteria were implemented to assess the quality of the included evidence base. The quality appraisal was performed by a single reviewer and checked by a second reviewer. Any differences between reviewers were settled via consensus. In situations where consensus could not be met, a third reviewer was consulted.

The quality and risk of bias tools used to appraise the included studies were dependent on the study design. RCTs were evaluated with the Cochrane Risk of Bias 2.0 (RoB 2.0) tool.[91] Deviating from the HTA protocol, the Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort Studies tool was used to appraise included NRSIs instead of the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool.[92-94]

The Grading of Recommendation, Assessment, Development and Evaluations (GRADE) approach was used to evaluate the quality of the evidence used to calculate the overall effect size for each of the 7 prioritised outcomes.[95,96] The 5 domains (imprecision, inconsistency, indirectness, risk of bias, publication bias) of the GRADE framework were scored (high, moderate, low, very low) according to a decision algorithm developed by Pollock et al.[95,97] The overall strength of the evidence (overall GRADE score) associated with the effect sizes for each outcome were presented in summary of findings (SoF) tables generated in GRADEpro.[96,98]

7.1.5 Data analysis of efficacy, effectiveness and safety outcomes

7.1.5.1 Data synthesis

De novo analyses were performed, as no existing systematic and meta-analyses met the inclusion criteria.

There were insufficient data points to perform mixed-effect meta-regression models, therefore pairwise meta-analyses that use random-effects models were used to compare PCI plus OMT or CABG plus OMT against OMT for both continuous and dichotomous outcomes reported by at least 2 studies. For the short-term benefits of PCI (plus OMT) and CABG (plus OMT) to be compared against the long-term

benefits of OMT, five timepoints—1 month (30 days), 12 months (1 year), 24 months (2 years), 50 months (5 years) and 120 months (10 years)—were used. These predetermined timepoints were selected following input from clinical experts and ICHOM guidance.[71] The 1-month timepoint was limited to reporting estimates for HRQoL.

Given that it is impossible to include the personalised nature of OMT into meta-analysis techniques, it was assumed that all OMT is equivalent between treatment groups and across trials. For the purpose of the clinical evaluation, the equivalency was extended to 2 scenarios: scenario 1 includes OMT prescribed before and after revascularisation; scenario 2 includes OMT prescribed alone compared to OMT prescribed alongside concurrent revascularisation.

Random-effects models were used to account for variation between the various combinations of surgical procedures (CABG, PCI [BMS, DES]) and medications (e.g. antiplatelet therapy and antianginals) in OMT.[81,99] A random-effects model was used to account for variations in the populations and interventions across the included studies.[81,99]

7.1.5.2 Continuous outcomes

Continuous outcomes were meta-analysed using meta package in R Studio.[100-102] Only one continuous outcome is included in the PICO (HRQoL), which was analysed as mean difference (MD) with 95% confidence intervals (CI). Standardised mean difference (SMD) was not used, as there was no difference in the measurement scales used to report HRQoL across individual studies. The meta-analysis was performed using random-effects models, with the inverse-variance method used to estimate between-study variance.

7.1.5.3 Dichotomous outcomes

Dichotomous outcomes were meta-analysed using meta package in R Studio.[100-102] The Mantel-Haenszel method was used to estimate primary study weights. Results were reported as RRs with 95% CI.

7.1.5.4 Assessment of heterogeneity

Heterogeneity and inconsistency were assessed statistically. Heterogeneity in continuous and dichotomous outcomes was measured using the Tau^2 and I^2 statistics. The I^2 statistic was interpreted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*—(0–40%: possibly not important; 30–60%: moderate heterogeneity; 50–90%: substantial; 75–100%: considerable heterogeneity).[81] The significance of I^2 was dependent on the strength of the evidence for heterogeneity (i.e. Tau^2) as well as direction and size of the measured effect.[81] In situations where considerable heterogeneity was evident, it was explored further.

The results were illustrated using forest plots, which provide a visual representation of effect sizes and corresponding uncertainties. The forest plots illustrated the individual timepoints in each included study as well as the overall effect, once adjusted for follow-up time.

7.1.5.5 Subgroup and sensitivity analysis

Subgrouping and meta-regressions could not be used to statistically explore potential causes of heterogeneity (e.g. high-risk patients), as none of the meta-analyses met the predetermined 10-trial threshold.[81]

Sensitivity analyses were used to investigate the impact that uncertainty and decisions made during the development of the review method had on the effect size of each outcome. Possible sources of uncertainty include risk of bias and imputed standard deviation (SD).[81]

A priori effect modifiers are listed below:[1]

Subgroup

- Comorbidities that classify CCS patients as high risk (i.e. cardiovascular comorbidities such as hypertension, valvular heart disease, heart transplantation; non-cardiovascular comorbidities including cancer, diabetes mellitus type 1 and 2, obesity, chronic kidney disease, age over 75 years)
- LMCA stenosis >50%
- LVEF ≤40%
- Refractory angina

Meta-regression

- Naïve revascularisation vs prior revascularisation with PCI
- Naïve revascularisation vs prior revascularisation with CABG
- Sex

Sensitivity analysis

- Imputed data SD
- Risk of bias due to missing outcomes
- Risk of bias due to publications bias
- Risk of bias due to selection bias

7.1.5.6 Assessment of publication bias

The risk of publication bias was not evaluated using funnel plot asymmetry as none of the meta-analyses met the predetermined 10-trial threshold.[81,103] Publication bias was assessed by searching clinical trial registries to identify unpublished trials.

7.1.5.7 Imputation methods for dealing with missing values

Missing SD values were imputed from available means, sample sizes, standard errors and 95% CI using formulas detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (*version 6.2*).[81]

Continuous values were combined using formulas detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)*.[81]

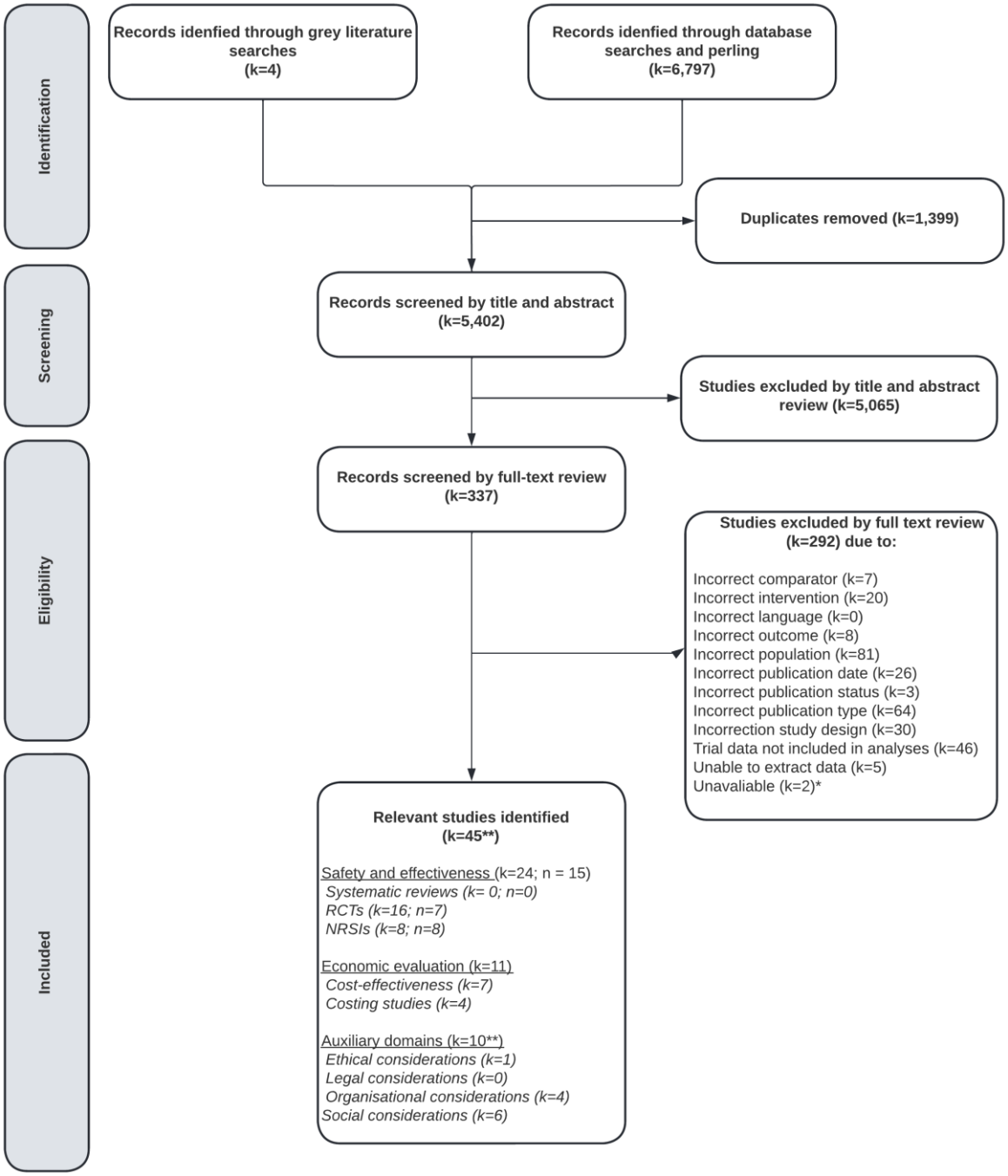
For studies that report outcomes graphically, *WebPlotDigitizer* was used to convert graph points into numerical values.[90]

7.2 Results: effectiveness, efficacy and safety

7.2.1 Search results

The systematic searches retrieved 6,797 records, including 8 through pearling and 4 identified via the grey literature. After removal of duplicates, 5,402 articles were screened by title and abstract, from which 337 were screened by full text and 45 met the inclusion criteria. The included studies comprised 7 unique RCTs (16 publications),[12,104-118] 8 cohort studies,[119-126] 11 economic evaluations,[127-137] and 10 studies relevant to the ethical, legal, social and organisational domains.[138-147] It is important to note that further publications pertaining to the 7 included RCTs have only been cited when usable data were extracted; in most cases the primary study publication was used as the basis for the evaluation. A list of all articles excluded after full-text review is available from the authors upon request. Existing systematic reviews did not meet the inclusion criteria, so none were included in the evaluation.

Figure 1 PRISMA flow diagram



Abbreviations

k: number of publications; **n**: number of trials; **NRSI:** nonrandomised studies of interventions; **RCT:** randomised control trial.

Notes

* These publications were not available.

** A single publication could be deemed relevant to multiple domains.

7.2.2 Study characteristics and risk of bias

7.2.2.1 RCT study characteristics

Seven randomised trials were included.[12,104-118] Pairwise comparisons were as follows: 3 trials compared PCI plus OMT against OMT;[107,108,110,117,118] 1 trial compared CABG plus OMT against OMT;[105,109,111,115,116] 2 trials compared revascularisation (either PCI or CABG) against OMT;[12,104,112] 1 trial used a 3-arm comparison comparing PCI plus OMT vs CABG plus OMT vs OMT.[106,113,114]

Study sizes ranged from 396 to 5,179 participants (median = 888, mean = 2,731) with the number of participants across all trials totalling 10,924.[12,104-118] The ISCHEMIA trial (n = 5,179) and ISCHEMIA–CKD trial (n = 777) were conducted in 37 countries,[12,104,112] the STICH trial (n = 1,212) in 22 countries,[105,109,111,115,116] the FAME 2 trial (n = 888) in 13 countries,[107,108,118] and the BARI 2D trial (n = 2,368) and EUROCTO trial (n = 396) in 6 countries.[106,113,114,117] The Hennigan 2020 trial (n = 104) was conducted at a single centre in Scotland.[110] Study duration ranged from 12 to 118 months, with the long-duration studies reporting outcome measures at multiple timepoints. All studies reported outcome data for all-cause mortality. Six trials reported outcome data for MACE, stroke and MI.[12,104-118] Three trials reported outcome data for quality of life.[110,111,117]

The aim of all studies was to assess the relative efficacy of invasive interventions (PCI or CABG) against OMT in people with CCS. ***Table 3*** summarises the study characteristics of the included studies.

Table 3 Characteristics of included RCTs assessing clinical effectiveness and safety of revascularisation

Study; trial; country	Study design; duration	Population	Intervention, sample size	Mean age (yrs) ± (SD)	Outcome(s)	Funding
BARI 2D, 2009[106,113,114] NCT00006305 6 countries [a]	RCT, multicentre 60 mo	CCS documented angiographically *and* type II diabetes mellitus	Total n = 2,368 • PCI (DES, BMS) + OMT n=798 • CABG + OMT n=378 • OMT n=1,192	• PCI (DES and BMS) + OMT 62.1 (9.0) • CABG + OMT 63.0 (8.5) • OMT 61.9 (9.3)	• All-cause mortality • MACE • MI • Stroke • Revascularisation	11 funders [b]
EUROCTO, 2018[117] NCT01760083 Europe (undetermined)	RCT, single-centre 12 mo	CCS including CTO	Total n = 396 • PCI (DES) + OMT n = 259 • OMT n = 137	• PCI (DES) + OMT 65.2 (9.7) • OMT 64.7 (9.9)	• All-cause mortality • Cardiac-specific HRQoL • General HRQoL • Hospitalisation • MI • MACE • Revascularisation • Stent thrombosis • Stroke	No industry sponsor
FAME 2, 2012[107,108,118] NCT00267774 Europe, North America	RCT, multicentre 7 mo, 24 mo, 60 mo	CCS eligible for PCI *and* >50% stenosis in major epicardial coronary artery	Total: n = 888 • PCI (DES) + OMT n = 447 • OMT n = 441	• PCI (DES) + OMT 63.52 (9.35) • OMT 63.86 (9.62)	• All-cause mortality • MACE • MI • Revascularisation • Stent thrombosis • Stroke	St. Jude Medical

Study; trial; country	Study design; duration	Population	Intervention, sample size	Mean age (yrs) ± (SD)	Outcome(s)	Funding
Hennigan et al., 2020[110] NCT02425969 UK	RCT, single-centre 3 mo, 12 mo	CCS	Total n = 104 • PCI (DES) + OMT n = 52 • OMT n = 52	• PCI (DES) + OMT 60 (8.00) • OMT 61 (9.00)	• All-cause mortality • Cardiac-specific HRQoL	Golden Jubilee National Hospital
ISCHEMIA, 2020[12,112] NCT01471522 37 countries [c]	RCT, multicentre 40 mo	CCS or moderate or severe ischaemia [e]	Total n = 5,179 • REV (PCI [DES, BMS, bioresorbable] & CABG) + OMT n = 2,588 • OMT n = 2,591	• REV + OMT 64 (8.90) • OMT 64 (8.90)	• All-cause mortality • Hospitalisation • Hospitalisation due to HF • MACE • MI • Stroke	National Health Institute (NIH) grant
ISCHEMIA–CKD[104] NCT01985360 37 countries [c]	RCT, multicentre 36 mo	CCS or severe ischaemia *and* CDK	Total: n = 777 • REV (PCI [DES, BMS, bioresorbable] & CABG) + OMT n = 388 • OMT n = 389	• REV + OMT 62 (10.38) • OMT 63 (10.45)	• All-cause mortality • Hospitalisation • Hospitalisation due to HF • MACE • MI • Stroke	National Heart, Lung and Blood Institute (NHLBI)
STICH, 2011[105,109,111,115,116] NCT00023595 22 countries [d]	RCT, multicentre 12 mo, 24 mo, 36 mo, 56 mo, 118 mo	CCS *and* HF, EF <35%	Total n = 1,212 • CABG + OMT n = 610 • OMT n = 602	• CABG + OMT 61 (10.38) • OMT 60 (10.38)	• All-cause mortality • Cardiac-specific HRQoL • General HRQoL • Hospitalisation • Hospitalisation due to HF • MACE • MI • REV • Stroke	National Heart, Lung, and Blood Institute (NHLBI); Abbott Laboratories

Abbreviations:

BMS: bare metal stent; **CABG:** coronary artery bypass; **CCS:** chronic coronary syndrome; **CDK:** chronic kidney disease; **CTO:** chronic total occlusion; **DES:** drug eluting stent; **EF:** ejection fraction; **HF:** heart failure; **HRQoL:**

health-related quality of life; **MACE:** major adverse cardiac events; **MI:** myocardial infarction; **mo:** month; **n:** sample size; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial; **REV:** revascularisation; **SD:** standard deviation.

Notes:

[a] Austria, Brazil, Canada, Czech Republic (Czechia) Mexico, USA.[106,113,114]

[b] National Heart, Lung and Blood Institute (NHLBI); National Institute of Diabetes and Digestive and Kidney Diseases; GlaxoSmithKline; Lantheus Medical Imaging; Astellas Pharma; Merck, Abbott Laboratories; Pfizer, MediSense, Bayer; Becton Dickinson; J.R. Carlson Labs; Centocor; Eli Lilly; LipoScience' Novartis; and Novo Nordisk.[106,113,114]

[c] Canada, USA, India, UK, Brazil, Poland, Russia, Spain, China, Italy, Singapore, Germany, Austria, Hungary, Serbia, Mexico, Australia, France, Lithuania, the Netherlands, Portugal, Argentina, New Zealand, Macedonia, Sweden, Israel, Japan, Belgium, Taiwan, South Africa, Egypt, Romania, Peru, Thailand, Malaysia.[12,112]

[d] Poland, India, Russia, Canada, USA, Serbia, Brazil, Australia, Germany, Italy, Hungary, UK, Thailand, Argentina, Sweden, Singapore, Austria, Lithuania, Norway, New Zealand, Malaysia.[105,109,111,115,116]

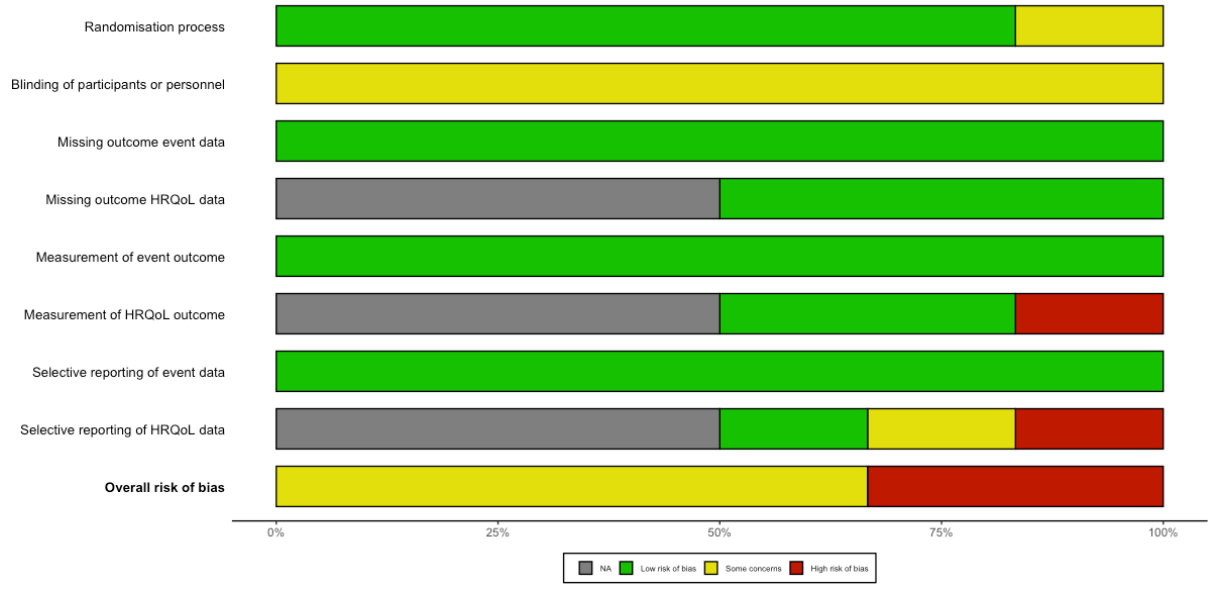
[e] Clinically indicated stress testing showed moderate or severe reversible ischaemia on imaging tests or severe ischaemia on exercise tests.[12,112]

- OMT assumed to be equivalent between trial arms.
- Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

7.2.2.2 RCT risk of bias

As assessed using the Cochrane RoB 2.0 tool, a summary of the risk of bias for all included trials is shown in ***Table 4***. All 7 trials reported randomisation methods; 6 trials reported methods to conceal allocation. In one study, allocation concealment was not reported.[106,113,114] Overall, the randomisation process was judged to be low risk. Blinding of participants was not feasible for invasive surgical procedures and, as such, this was judged as of some concern. Missing outcome data events and missing outcome data from HRQoL, and measurement of the outcome event were judged as low risk of bias. For measurement of HRQoL the overall judgement was low risk of bias, although one study (EUROCTO 2018) was judged as being at high risk of bias due to non-blinded patient self-assessment.[117] Selective reporting of events was judged to be low risk across studies. Selective reporting for HRQoL was judged to be low risk in 2 studies, of some concern in the Hennigan 2020 study due to unpublished post-hoc data analysis,[110] and high risk in the ISCHEMIA 2020 study due to the post-hoc analysis used.[12,112] Overall risk of bias was judged to be of some concern in 5 studies and high risk in 2 studies.[12,104-118]

Figure 2 Risk of bias graph for RCTs assessing clinical outcomes combined (n = 7 RCTs)



Abbreviations:
HRQoL: health-related quality of life; **NA:** not applicable; **RCT:** randomised control trial.
Notes:

- NA is used to indicate when a trial did not report HRQoL data.
- Regarding the appraisal of 'missing outcome', 'measurement of outcome', and 'selective reporting', dichotomous event outcomes and continuous HRQoL outcomes were appraised separately to account for the differing nature of collecting, measuring and reporting dichotomous and continuous data.

Table 4 Risk of bias summary for clinical outcomes in the RCTs

Study	Randomisation process	Blinding of participants/ personnel	Missing outcome data (event)	Missing outcome data (HRQoL)	Measurement of the outcome (event)	Measurement of the outcome (HRQoL)	Selective reporting (event)	Selective reporting (HRQoL)	Overall
BARI 2D, 2009[106,113,114]	-	-	+	NA	+	NA	+	NA	-
EUROCTO, 2018[117]	+	-	+	+	+	X	+	+	X
FAME 2, 2012 [107,108,118]	+	-	+	NA	+	NA	+	NA	-
Hennigan et al., 2020[110]	+	-	+	+	+	+	+	-	-
ISCHEMIA, 2020[12,112]	+	-	+	+	+	+	+	X	X
ISCHEMIA–CKD, 2020[104]	+	-	+	NA	+	NA	+	NA	-
STICH, 2011[105,106,111,115,116]	+	-	+	+	+	+	+	+	-

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+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations:

HRQoL: health-related quality of life; **NA:** not applicable; **RCT:** randomised control trial.

Notes:

- Regarding the appraisal of 'missing outcome', 'measurement of outcome', and 'selective reporting', dichotomous event outcomes and continuous HRQoL outcomes were appraised separately to account for the differing nature of collecting, measuring and reporting dichotomous and continuous data.
- NA is used to indicate when a trial did not report HRQoL data.

7.2.2.3 NRSI study characteristics

Table 5 summarises the study characteristics of the included NRSIs. In total, 8 NRSI single-country studies were included, with a total of 25,803 participants.[119-126] Study size ranged from 83 to 9,676 participants. Studies were conducted in North America and Europe, including the USA (k = 4), Canada (k = 1), UK (k = 2) and Italy (k = 1). Six studies used a retrospective study design and two used a prospective study design.[119-126] Average study duration varied across studies, ranging from 12 months to 84 months.[119-126]

Five studies compared PCI plus OMT against OMT, 2 studies compared revascularisation plus OMT against OMT and 1 study compared PCI plus OMT vs CABG plus OMT vs OMT.[119-126]

All included studies enrolled participants with CCS.[119-126] Seven studies reported all-cause mortality, 4 studies reported MACE, 3 reported hospitalisation rates, 4 reported revascularisation rates and 3 studies reported rates of MI.[119-126]

Table 5 Characteristics of included NRSIs assessing clinical effectiveness and safety of revascularisation

Study; trial; country	Study design; treatment duration	Population	Intervention (sample size)	Mean age (yrs) ± SD	Outcome(s)	Funding
Anderson et al. 2016[119] USA	Retrospective cohort, multicentre 25 mo	CCS *and* syncope	Total n = 7,338 PCI (DES) + OMT n = 3,196 OMT n = 4,142	PCI (DES) + OMT 77 (8.15) OMT 77 (8.15)	• All-cause mortality • Hospitalisation • MI	American College of Cardiology National Cardiovascular Data Registry
Castleberry et al. 2014[120] USA	Retrospective cohort, single-centre 65 mo	CCS • >75% lesion in at least 1 coronary vessel *and* • moderate or severe MR (>2)	Total n = 4,989 PCI (DES) + OMT n = 1,295 CABG + OMT n = 1,651 OMT n = 1,800	PCI (DES) + OMT 65 (13.34) CABG + OMT 66 (11.12) OMT 68 (12.60)	• All-cause mortality	No trial sponsor
Danson et al. 2019[121] UK	Retrospective cohort, NR 12 mo	CCS • referred for REV via CABG *and* • deemed unsuitable for CABG by 2 surgeons	Total n = 248 PCI (DES) + OMT n = 131 OMT n = 117	PCI (DES) + OMT NR OMT NR	• MACE	No trial sponsor

Study; trial; country	Study design; treatment duration	Population	Intervention (sample size)	Mean age (yrs) ± SD	Outcome(s)	Funding
Hannan et al. 2012[122] USA	Retrospective cohort, multicentre 34 mo	CCS	Total n = 1,866 PCI (DES, BMS, undetermined) + OMT n = 933 OMT n = 933	PCI (DES, BMS, undetermined) + OMT 66.3 (11.2) OMT 66.6 (11.1)	• All-cause mortality • Hospitalisation • MACE • MI • REV	New York State Department of Health
Ladwiniec et al. 2015[123] UK	Prospective cohort, Single-centre 60 mo	CCS • including CTO	Total n = 588 PCI (DES, BMS) + OMT n = 294 OMT n = 294	PCI (DES, BMS) + OMT 64.3 (10.0) OMT 63.9 (10.2)	• All-cause mortality • MACE • REV	The Hull & East Yorkshire Cardiac Trust Fund
Phan et al. 2021[123] USA	Retrospective cohort, Single-centre 42 mo	CCS	Total n = 1,015 REV + OMT 557 • PCI (undetermined) + OMT n = 418 • CABG + OMT n = 139 OMT n = 458	REV + OMT 83.5 (2.8) OMT 83.7 (3.0)	• All-cause mortality • Hospitalisation • REV • MI	No trial sponsor
Prestipino et al. 2016[125] Italy	Retrospective cohort, Single-centre 79 mo, 87 mo	CCS • multi-vessel disease *and* • ineligible for PCI *and*	Total n = 83 PCI (DES) + OMT n = 42 OMT n = 41	PCI (DES) + OMT 77.9 (4.1) OMT 80.1 (4.8)	• All-cause mortality • MACE	NR

Study; trial; country	Study design; treatment duration	Population	Intervention (sample size)	Mean age (yrs) ± SD	Outcome(s)	Funding
		• other qualifying criteria [a]				
Wijeysundera et al. 2014[126] Canada	Prospective cohort, Single-centre 3 mo, 30 mo	CCS • stenosis >70% *or* • LCMA >50%	Total n = 9,676 REV (PCI [undetermined] & CABG) + OMT n = 4,838 OMT n = 4,838	REV + OMT 65.87 (10.15) OMT 65.77 (10.17)	• All-cause mortality • REV • Stent thrombosis • TVR	Canadian Institute of Heath Research (CIHR); Schulich Heart Centre

Abbreviations:

BMS: bare metal stent; **CABG:** coronary artery bypass; **CCS:** chronic coronary syndrome; **CTO**: chronic total occlusion; **DES:** drug eluting stent; **HRQoL:** health-related quality of life; **LCMA:** left main coronary artery stenosis; **MACE:** major adverse cardiac events; **MI:** myocardial infarction; **mo:** month; **n:** sample size; **MR:** mitral regurgitation; **NA:** not applicable; **NR:** not reported; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **REV:** revascularisation; **SD:** standard deviation; **TVR:** target vessel revascularisation; **yr:** year.

Notes:

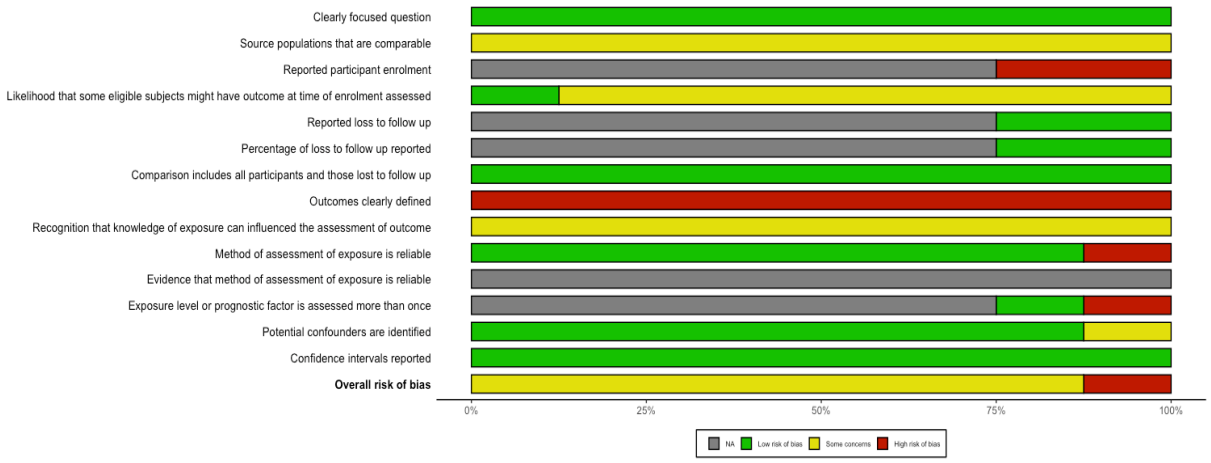
[a] Other qualifying criteria included EuroSCORE II >6% and at least 1 of the following risk factors: obesity (body mass index >30 kg/m^2); chronic renal failure (creatinine clearance <40 mL/min); age (>80 yrs); carotid artery disease (internal carotid artery stenosis >65%); neurological risk factors (i.e. cortical vascular ischaemic disease, stroke within last 90 days); haematological risk (i.e. haemoglobin <10 g/dL, platelet count <100,000 /µL); and cardiologic risk factors (i.e. ejection fraction <30%, ejection fraction <40% associated with moderate MR, dyspnoea and chest pain at rest).[125]

- OMT assumed to be equivalent between trial arms.
- Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

7.2.2.4 NRSI risk of bias

As assessed using the SIGN risk of bias tool for cohort studies, the overall study quality was judged as acceptable in 7 of the 8 studies.[92,93] One study was judged to be at unacceptable risk of bias.[119] Due to patient enrolments being nonrandomised, the 2 groups were not comparable for all the reported baseline characteristics except for 1 study.[125] It is unclear how many of the participants were entered into the study, and the risk of selection bias is unknown. It is unclear whether some of the participants had outcomes at the start of the study, and if these were adjusted in the analysis, leaving the studies at risk of performance bias.[126] Most studies did not report study attrition. Similarly, most studies did not report how the type of intervention affected study attrition. Outcomes were clearly defined and unlikely to be misclassified between studies. None of the study interventions were blind to patients or medical staff, and it is unclear if this was acknowledged as a potential source of bias influencing outcomes. The method of assessment was judged to be reliable for most outcome measures (e.g. death, MI, hospitalisation), except in the study by Wijeysundera et al. 2014 where HRQoL was not clearly reported.[126] Potential confounders were adjusted by all studies using methods such as propensity score matching; CI values were reported.[119-126] For further details of individual studies see ***Table 6***.

Figure 3 Risk of bias graph for NRSIs assessing clinical outcomes combined (n = 8 NRSIs)



Abbreviations:
NA: not applicable; **NRSI:** nonrandomised studies of interventions.
Notes:
None of the included NRSIs reported usable continuous HRQoL data that was controlled for measured confounders.

Table 6 Risk of bias summary for clinical effectiveness outcomes in NRSIs

Item	Anderson et al. 2016 [119]	Castleberry et al. 2014 [120]	Danson et al. 2019 [121]	Hannan et al. 2012 [122]	Ladwiniec et al. 2015 [123]	Phan et al. 2021 [124]	Prestipino et al. 2016 [125]	Wijeysundera et al. 2014 [126]
1.1 -- The study addresses an appropriate and clearly focused question.	+	+	+	+	+	+	+	+
1.2 [a] -- The 2 groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	-	-	-	-	-	-	-	-
1.3 [b] -- The study indicates how many of the people asked to take part did so, in each of the groups being studied.	NA	NA	NA	NA	X	NA	NA	X
1.4 -- The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	-	-	-	-	-	-	-	+
1.5 [b] -- What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	NA	NA	NA	NA	0%	NA	NA	0%
1.6 [b] -- Comparison is made between full participants and those lost to follow-up, by exposure status.	NA	NA	NA	NA	+	NA	NA	+
1.7 -- The outcomes are clearly defined.	+	+	+	+	+	+	+	+
1.8 [a] -- The assessment of outcome is made blind to exposure status.	X	X	X	X	X	X	X	X
1.9 -- Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	-	-	-	-	-	-	-	-
1.10 -- The method of assessment of exposure is reliable.	+	+	+	+	+	+	+	X
1.11 [c] -- Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	NA	NA	NA	NA	NA	NA	NA	NA
1.12 [b] -- Exposure level or prognostic factor is assessed more than once.	NA	NA	NA	NA	X	NA	NA	-
1.13 -- The main potential confounders are identified and taken into account in the design and analysis.	-	+	+	+	+	+	+	+
1.14 -- Have confidence intervals been provided?	+	+	+	+	+	+	+	+
2.1 -- Overall assessment of the study.	**(0)**	**(+)**	**(+)**	**(+)**	**(+)**	**(+)**	**(+)**	**(+)**

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+ = yes; **x** = no; **-** = can't say; **(+ +)** = high quality; **(+)** = acceptable; **(0)** = unacceptable

Abbreviations:

NA: not applicable; **NRSI:** nonrandomised studies of interventions.

Notes:

[a] only applies when there is a compactor.

[b] only applied when the trial is prospective.

[c] only applies when a subjective measure is used.

- Risk of bias was appraised using an adapted version of the *Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort Studies*.[92,93]
- None of the included NRSIs reported continuous HRQoL data that was controlled for measured confounders.

7.3 Applicability of evidence to Switzerland

Applicability refers to the generalisability of the included studies to the Swiss context. It involves comparing demographics and clinical characteristics in the included studies to that which generally occurs in Swiss practice.

There is limited published literature reporting demographic characteristics of Swiss CCS patients; however, the demographic variables shown in ***Table 7*** are broadly consistent with the PICO criteria for this HTA report. The average age of participants in the trials was similar to the mean age of the Swiss population with CCS. BMI scores were similar to the Swiss population (i.e. overweight: BMI 25 to <30), although 1 trial (BARI 2D) enrolled participants with an average BMI >30 (i.e. obese). One trial (BARI 2D) included participants who all were diagnosed with diabetes. The other 6 trials included a proportion of participants with type II diabetes (20% to 56%), compared with the average Swiss cohort of 29%. Male/Female ratios in the trials were higher for men (56–83% male), corresponding with Swiss demographic data. The 7 included RCTs were primarily undertaken in multicentre sites across North America and Europe, with some smaller studies contributing data from Australia, Brazil, India, China, Singapore, Mexico, Argentina, New Zealand, Taiwan and Japan. No studies were fully conducted in Switzerland. The European studies are more applicable to the Swiss context, owing to similarities in population and clinical practice. A Swiss study of a CCS population in 2008 found almost all patients were prescribed antiplatelet therapy (98.6%).[70] Statins (84%), beta-blockers (75%), calcium antagonists (34%) and nitrates (51%) were also commonly administered.[70] A notable exception in the Swiss care pathway is the absence of warfarin, whereas some of the trial data included patients receiving warfarin. The Swiss care pathway uses different vitamin K antagonists (i.e. phenprocoumon and acenocoumarol).

PCI is performed in hospital and outpatient settings in Switzerland, but it was unclear, due to limited descriptions, if hospital and outpatient departments were used in the RCTs. Evidence from 1 study comparing outpatient and inpatient PCI in patients with left main disease found no difference in MACE at 30 days or 5 years follow-up, although outpatients were less likely to have experienced recent MI.[148]

BMS were used in some participants in the RCTs evaluating PCI interventions. Multigeneration stents were used within studies as newer stent technology became available. In the Swiss context, 99% of the stents implanted in Switzerland (2019) are DES.[149] None of the trials included participants revascularised exclusively with third generation DES. Results from a network meta-analysis found that new generation DES, but not bare-metal stents or early generation DES, are associated with improved

survival compared with initial OMT.[150] Trials prior to 2010 were also included, using CABG procedures that may not reflect contemporary practice.

Table 7 Summary table characterising the Swiss context for the treatment of CCS

Parameter	Characteristics
Demographics	• Female gender with CCS = 670/1818 (36.9%) • Mean age patients with CCS = 66.98 ±10.04 (2018)[151] • Mean BMI kg/m2 in patients with CCS = 28.95 ± 4.78 • Mean systolic blood pressure in patients with CCS = 134.98 mmHg ±18.80 • Mean diastolic blood pressure in patients with CCS = 79.64 mmHg ±11.02 • Mean heart rate in patients with CCS = 72.44 ±13.16 BPM • Diabetes mellitus in patients with CCS = 528/1818 (29.0%) • HBA1c > 7% or fasting glucose > 7 mmol/l in patients with CCS = 377/1546 (24.4%) • Smoking status: o Current in patients with CCS =344/1818 (18.9%) o Former, >1 year in patients with CCS= 436/1818 (24.0%) • History of heart failure in patients with CCS= 691/1818 (38.0%) • History of atrial fibrillation in patients with CCS = 286/1818 (15.7%) • Previous stroke/TIA in patients with CCS = 124/1818 (6.8%) • Chronic kidney disease in patients with CCS = 92/1798 (5.1%) • Total cholesterol in patients with CCS = 4.81mmol/l ±1.30 • LDL (> 2.59 mmol/l) in patients with CCS = 2.87mmol/l ±1.14 • Triglycerides, in patients with CCS = 1.66 mmol/l ±0.96 • Hb1Ac >7%, in patients with CCS =139/235 (59.1%) • In-hospital mortality rate following PCI for CCS 0.2%[33]
Intervention	• PCI (DES) o DES used 99% of PCI • CABG
Comparator	**Optimal Medical Therapy** Antiplatelet therapy Oral P2Y12 inhibitors: e.g. Prasugrel; Ticagrelor Vitamin K antagonist: e.g. Acenocoumarol; Phenprocoumon Anti-anginal therapy (Beta-blockers): e.g. Metoprolol, Bisoprolol Anti-anginal therapy (Calcium channel blockers): e.g. Amlodipine, Verapamil, Diltiazem Nitrates: e.g. Nicorandil, Nitroglycerin Renin angiotensin system blockers: ACE inhibitors: e.g.Captopril; Enalapril; Fosinopril; Lisinopril; Perindopril; Quinapril; Ramipril ARB inhibitors: e.g. Candesartan; Losartan; Telmisartan; Valsartan Lipid-lowering therapy Statins: e.g. Atorvastatin; Rosuvastatin; Simvastatin; Pravastatin; Fluvastatin; Pitavastatin; Pravastatin Other lipid lowering therapy: e.g. Ezetimibe; Evolocumab; Alirocumab
Setting	Hospital and outpatient department

Abbreviations:
ACE: angiotensin-converting enzyme inhibitors; **ARB**: angiotensin receptor blockers; **BPM**: beats per minute; **CABG**: coronary artery bypass graft; **CAD**: coronary arterial disease; **CCS**: chronic coronary syndrome; **DES:** drug-eluting stents; **PCI**: percutaneous coronary intervention.

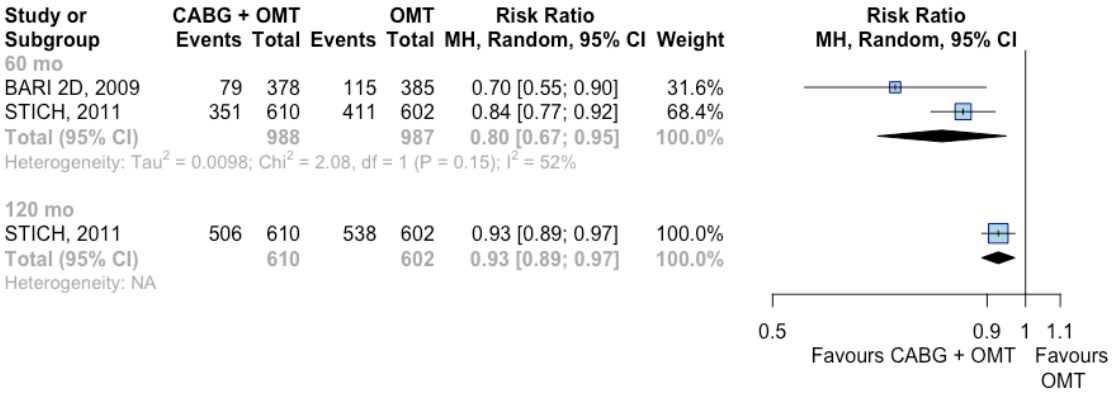
7.4 Clinical effectiveness findings

7.4.1 MACE: RCT evidence

7.4.1.1 CABG plus OMT vs OMT alone

For MACE, 2 studies reported significantly lower rates in the CABG plus OMT group compared to OMT alone at 60 months follow-up.[114-116] Heterogeneity was moderate. Longer follow-up at 120 months also significantly favoured CABG plus OMT over OMT alone (***Figure 4***).

Figure 4 Risk ratio of MACE for CABG plus OMT compared to OMT alone, 60–120 months (RCTs)

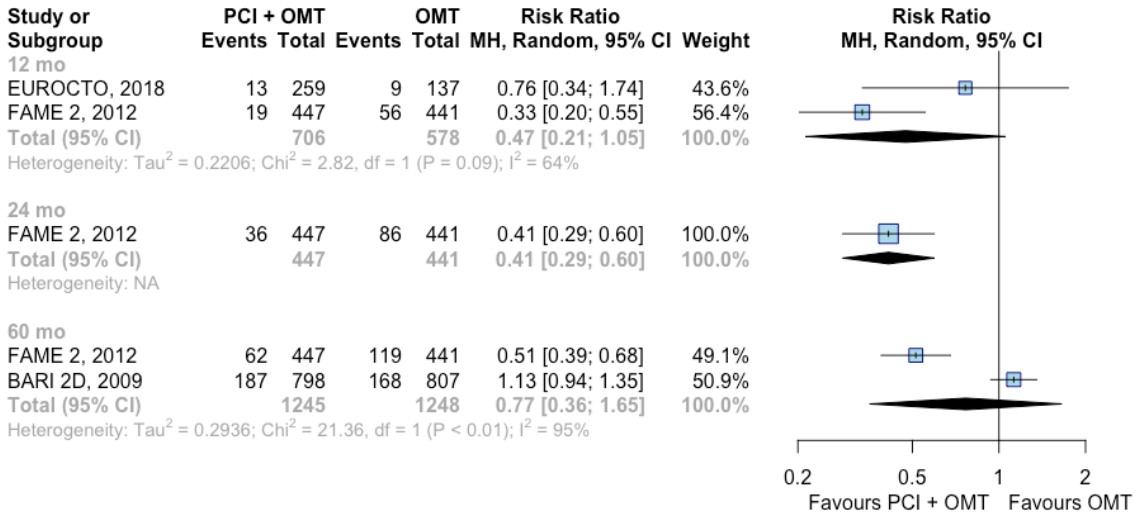


Abbreviations
CABG: coronary artery bypass; **CI:** confidence interval; **MACE:** major adverse cardiac events; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial.
Notes
- OMT assumed to be equivalent between trial arms.
- MACE defined as all-cause mortality, MI, stroke and/or hospitalisation.

7.4.1.2 PCI plus OMT vs OMT alone

For MACE at 12 months, 2 studies reported no significant difference between PCI plus OMT vs OMT alone.[107,108,114-116,118] Heterogeneity was substantial. At 24 months, 1 study reported significantly lower rates of MACE in the PCI plus OMT group compared to OMT alone. However, 2 studies found longer follow-up at 60 months was not significantly different between participants receiving PCI plus OMT and OMT alone. Heterogeneity was considerable between the 2 studies, with the FAME 2 study favouring the PCI group. In the BARI 2D study, all participants had type II diabetes (***Figure 5***).

Figure 5 Risk ratio of MACE for PCI plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CI: confidence interval; **MACE:** major adverse cardiac events; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial.

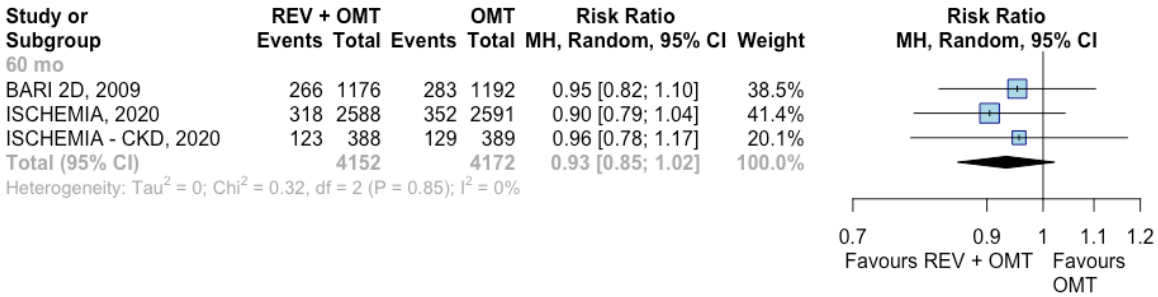
Notes

- OMT assumed to be equivalent between trial arms.
- MACE defined as all-cause mortality, MI, stroke and/or hospitalisation.

7.4.1.3 Revascularisation and OMT vs OMT alone

In 3 studies, no significant differences in MACE were found between revascularisation plus OMT and OMT alone at 60 months follow-up. Heterogeneity was low (***Figure 6***).[12,104,106,112-114]

Figure 6 Risk ratio of MACE for revascularisation plus OMT compared to OMT alone, 60 months (RCTs)



Abbreviations

CI: confidence interval; **MACE:** major adverse cardiac events; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial; **REV:** revascularisation.

Notes

- OMT assumed to be equivalent between trial arms.
- MACE defined as all-cause mortality, MI, stroke and/or hospitalisation.
- Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

7.4.2 MACE: NRSI evidence

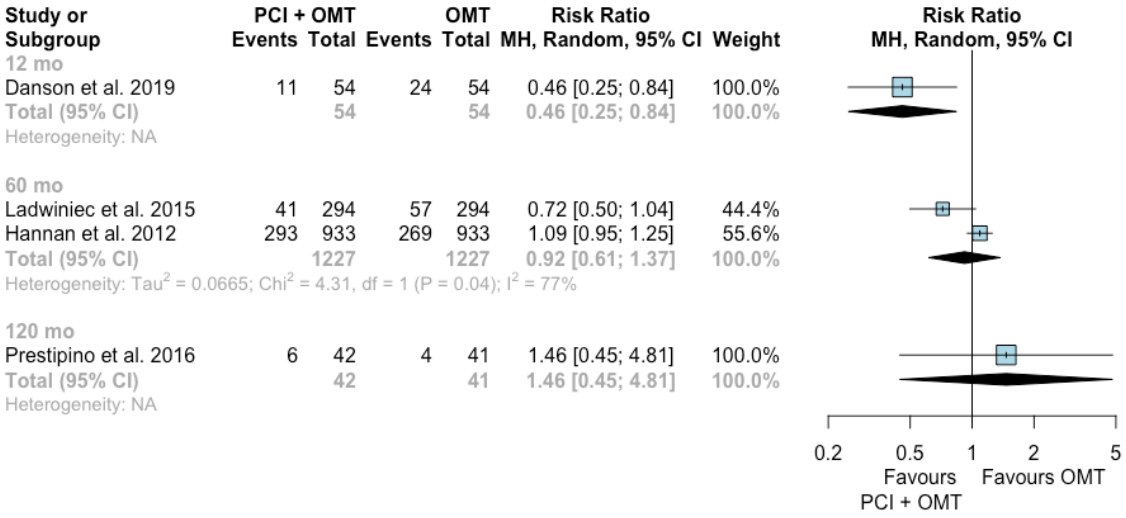
7.4.2.1 CABG plus OMT vs OMT alone

None of the included NRSIs that controlled for measured confounders reported MACE outcomes for a comparison of CABG plus OMT and OMT alone.

7.4.2.2 PCI plus OMT vs OMT alone

In one small NRSI, MACE outcomes at 12 months were significantly lower in the PCI plus OMT group compared to OMT alone.[121-123,125] Two studies reported MACE at 60 months; no significant differences were found between PCI plus OMT and OMT alone. Heterogeneity was considerable. One study reported MACE at 120 months; no significant differences were found between interventions (***Figure 7***).

Figure 7 Risk ratio of MACE for PCI plus OMT compared to OMT alone, 12–120 months (NRSIs)



Abbreviations

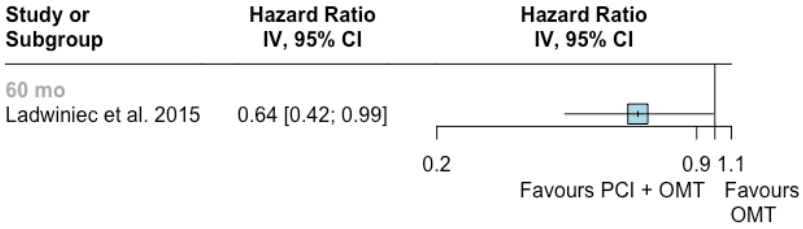
CI: confidence interval; **MACE:** major adverse cardiac events; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

Notes

- OMT assumed to be equivalent between trial arms.
- MACE defined as all-cause mortality, MI, stroke and/or hospitalisation.
- All included NRSIs controlled for measured confounders.

One study observed that the HR for MACE was significantly lower for participants in the PCI plus OMT group compared to OMT alone at 60 months follow-up (***Figure 8***).

Figure 8 Hazard ratio of MACE for PCI plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CI: confidence interval; **IV:** inverse variance; **MACE:** major adverse cardiac events; **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

Notes

- OMT assumed to be equivalent between trial arms.
- MACE defined as all-cause mortality, MI, stroke and/or hospitalisation.
- All included NRSIs controlled for measured confounders.

7.4.2.3 Revascularisation plus OMT vs OMT alone

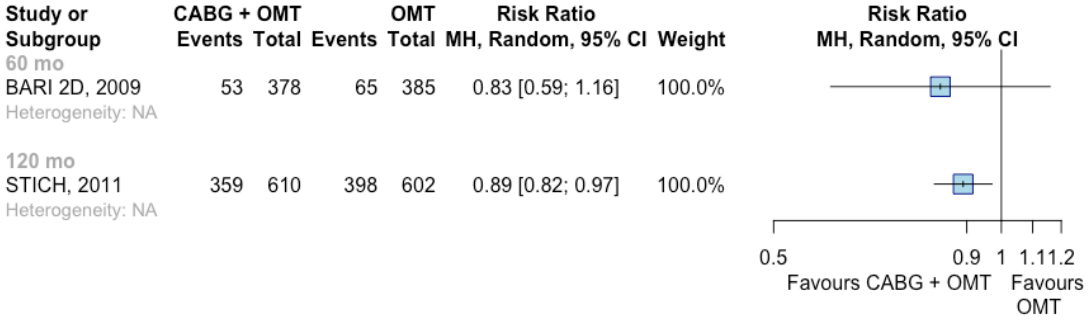
None of the included NRSIs that controlled for measured confounders, reported MACE outcomes for a comparison of revascularisation plus OMT and OMT.

7.4.3 All-cause mortality: RCT evidence

7.4.3.1 CABG plus OMT vs OMT alone

All-cause mortality reported in 1 study at 60 months follow-up was not significantly different between CABG plus OMT and OMT alone.[114,116] Certainty of evidence was low. At 120 months follow-up, all-cause mortality was significantly lower in the CABG plus OMT group compared to OMT alone (***Figure 9***).

Figure 9 Risk ratio of all-cause mortality for CABG plus OMT compared to OMT alone, 60–120 months (RCTs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial.

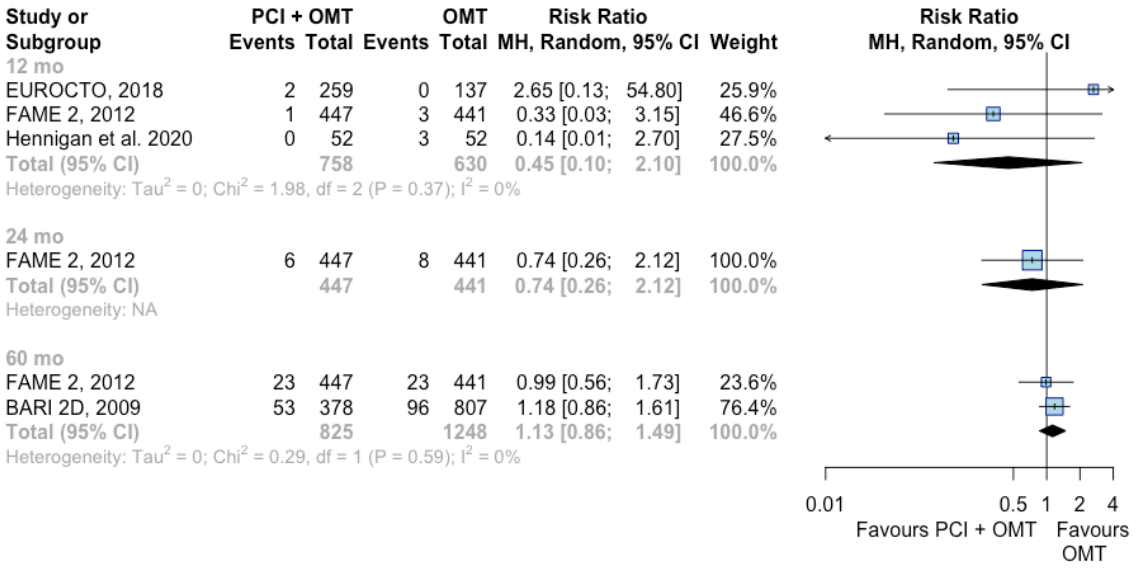
Notes

- OMT assumed to be equivalent between trial arms.

7.4.3.2 PCI plus OMT vs OMT alone

At 12 months follow-up, 3 studies found no significant differences between PCI plus OMT and OMT alone for all-cause mortality.[107,108,114,117,118] Heterogeneity was low. At 24 months, 1 study observed no significant difference between PCI plus OMT and OMT alone. At 60 months follow-up, 2 studies observed no significant difference between PCI plus OMT and OMT alone. Heterogeneity was low and certainty of evidence was moderate (***Figure 10***).

Figure 10 Risk ratio of all-cause mortality for PCI plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial.

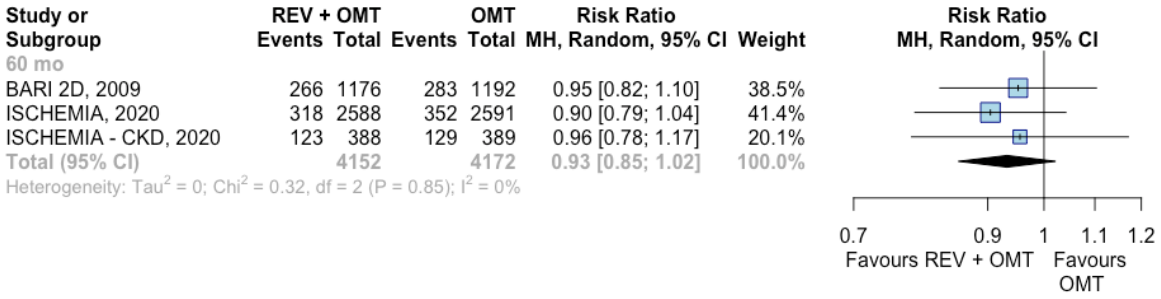
Notes

- OMT assumed to be equivalent between trial arms.

7.4.3.3 Revascularisation plus OMT vs OMT alone

There was no significant difference in all-cause mortality from 3 studies at 60 months follow-up.[12,104,114] Heterogeneity was low and certainty of evidence was high (***Figure 11***).

Figure 11 Risk ratio of all-cause mortality for revascularisation plus OMT compared to OMT alone at 60 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial; **REV:** revascularisation.

Notes

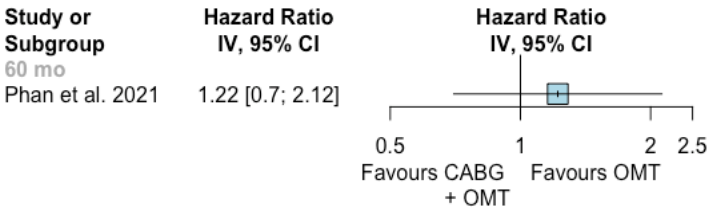
- OMT assumed to be equivalent between trial arms.
- Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

7.4.4 All-cause mortality: NRSI evidence

In one study, the all-cause mortality HR was not significantly different between CABG plus OMT and OMT alone at 60 months follow-up (***Figure 12***).[124]

7.4.4.1 CABG plus OMT vs OMT alone

Figure 12 Hazard ratio of all-cause mortality for CABG plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **IV:** inverse variance; **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy.

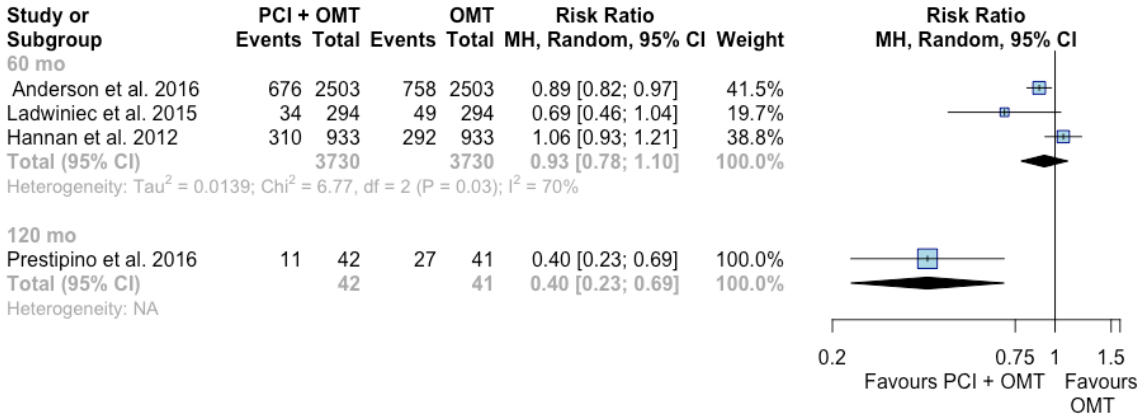
Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

7.4.4.2 PCI plus OMT vs OMT alone

In 3 studies that reported follow-up data at 60 months, no significant differences were found in all-cause mortality between PCI plus OMT and OMT alone.[119,122,123,125] Heterogeneity was substantial. One study found all-cause mortality was significantly lower in the PCI plus OMT group compared to OMT alone at 120 months follow-up (***Figure 13***).

Figure 13 Risk ratio of all-cause mortality for PCI plus OMT compared to OMT alone, 60–120 months (NRSIs)



Abbreviations

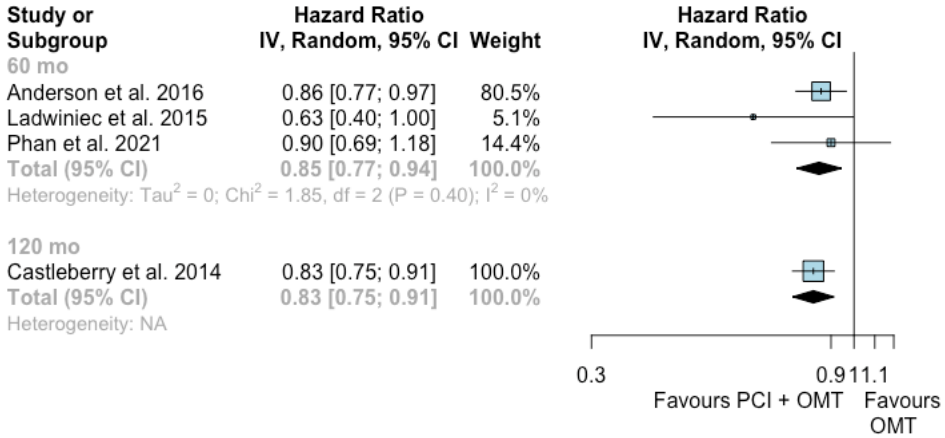
CI: confidence interval; **MH:** Mantel-Haenszel method **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

The HR for all-cause mortality in 3 studies was significantly lower in the PCI plus OMT group compared to OMT alone at 60 months follow-up.[119,120,123,124] Heterogeneity was low. Longer-term follow-up (120 months) in 1 study was also significantly lower in the PCI plus OMT group compared to OMT alone (***Figure 14***).

Figure 14 Hazard ratio all-cause mortality for PCI plus OMT compared to OMT alone 60–120 months (NRSIs)



Abbreviations

CI: confidence interval; **IV:** inverse variance; **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

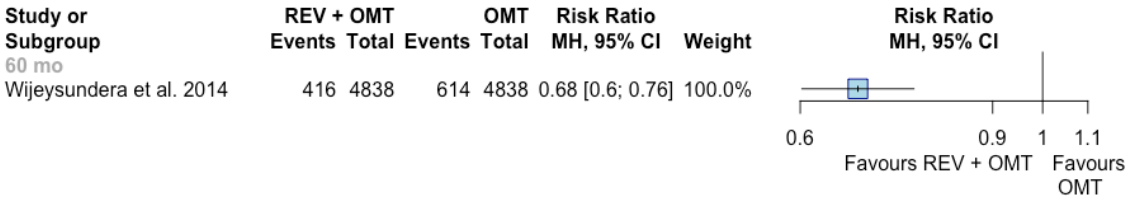
Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

7.4.4.3 Revascularisation plus OMT vs OMT alone

All-cause mortality was significantly lower in participants receiving revascularisation plus OMT compared to OMT alone at 60 months follow-up (***Figure 15***).[126]

Figure 15 Risk ratio of all-cause mortality for revascularisation plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

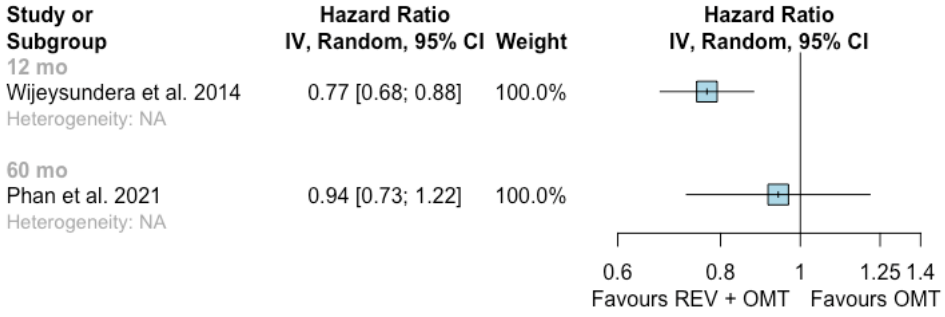
CI: confidence interval; **MH:** Mantel-Haenszel method **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **REV:** revascularisation.

Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

All-cause mortality HR at 12 months follow-up in 1 study was significantly lower in the revascularisation plus OMT group compared to OMT alone.[126] However, all-cause mortality at 60 months in 1 study was not significantly different between revascularisation plus OMT and OMT alone (***Figure 16***).[124]

Figure 16 Hazard ratio all-cause mortality for revascularisation plus OMT compared to OMT alone, 12–60 months (NRSIs)



Abbreviations

CI: confidence interval; **IV:** inverse variance; **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **REV:** revascularisation.

Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

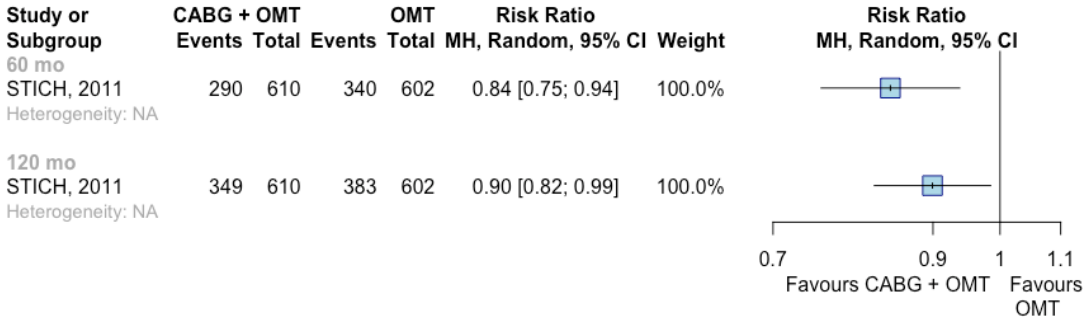
7.4.5 Hospitalisation: RCT evidence

7.4.5.1 CABG plus OMT vs OMT alone

Hospitalisation rates from 1 study were significantly lower in participants receiving CABG plus OMT compared with OMT alone at 60 months follow-up,[105] indicating 9 fewer hospitalisations per 100 patients

than OMT alone (***Table 8***). Certainty of evidence was high. Follow-up hospitalisation rates at 120 months were also significantly lower in participants receiving CABG plus OMT compared with OMT alone (***Figure 17***).[116]

Figure 17 Risk ratio of hospitalisation for CABG plus OMT compared to OMT alone, 60–120 months (RCTs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial.

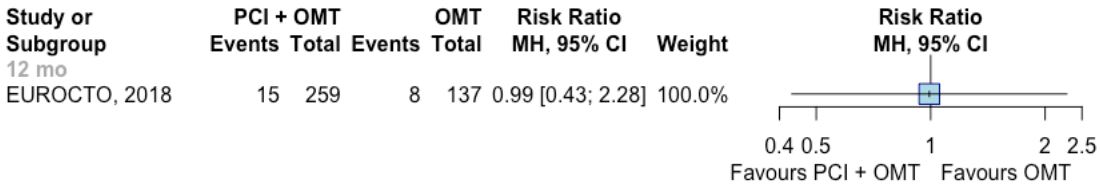
Notes

- OMT is assumed to be equivalent between trial arms.
- Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

7.4.5.2 PCI plus OMT vs OMT alone

Hospitalisation rates from 1 study were not significantly different between participants receiving PCI plus OMT and OMT alone at 12 months follow-up.[117] Certainty of evidence was low (***Figure 18***).

Figure 18 Risk ratio of hospitalisation for PCI plus OMT compared to OMT alone at 12 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial.

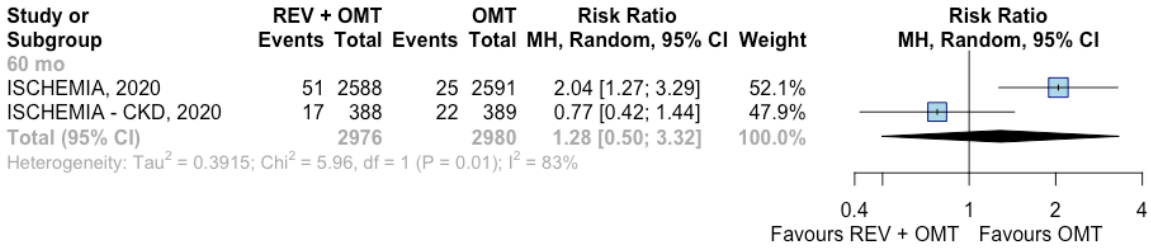
Notes

- OMT assumed to be equivalent between trial arms.
- Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

7.4.5.3 Revascularisation plus OMT vs OMT alone

Hospitalisation rates from 2 studies were not significantly different for revascularisation plus OMT compared with OMT alone at 60 months follow-up.[12,104] Heterogeneity was considerable. Certainty of evidence was very low. The ISCHEMIA 2020 trial favoured OMT. The heterogeneity and the difference in direction of treatment effect may be due to the ISCHEMIA–CKD 2000 trial including a subpopulation of patients with chronic kidney disease (***Figure 19***).

Figure 19 Risk ratio of hospitalisation for revascularisation plus OMT compared to OMT alone at 60 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial; **REV:** revascularisation.

Notes

- OMT assumed to be equivalent between trial arms.
- Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.
- Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

7.4.6 Hospitalisation: NRSI evidence

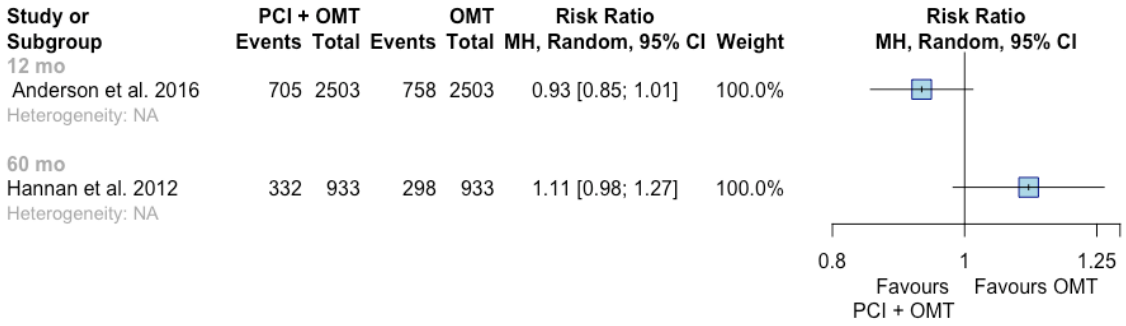
7.4.6.1 CABG plus OMT vs OMT alone

None of the included NRSIs that controlled for measured confounders reported hospitalisation outcomes for a comparison of CABG plus OMT and OMT.

7.4.6.2 PCI plus OMT vs OMT alone

Hospitalisation rates in 1 study were not significantly different between PCI plus OMT compared to OMT alone at 12 and 60 months follow-up (***Figure 20***).[119,122]

Figure 20 Risk ratio of hospitalisation for PCI plus OMT compared to OMT alone, 12–60 months (NRSIs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

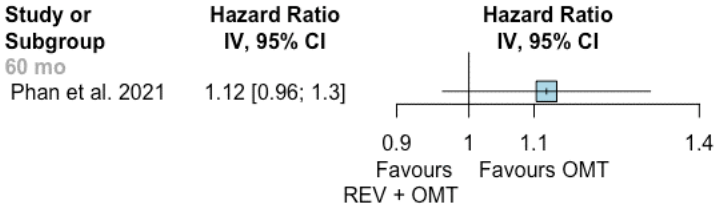
Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.
- Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

7.4.6.3 Revascularisation plus OMT vs OMT alone

Hospitalisation rates were not significantly different between revascularisation plus OMT and OMT alone in 1 study at 60 months follow-up (***Figure 21***).[124]

Figure 21 Hazard ratio hospitalisation for revascularisation plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CI: confidence interval; **IV:** inverse variance; **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy.

Notes

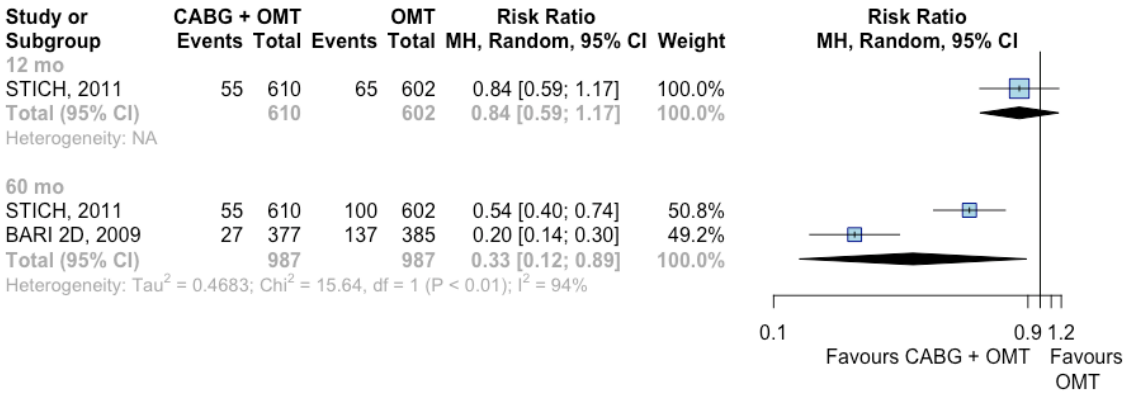
- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.
- Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

7.4.7 Subsequent revascularisation: RCT evidence

7.4.7.1 CABG plus OMT vs OMT alone

The need for subsequent revascularisation was not significantly different between CABG plus OMT compared to OMT alone at 12 months follow-up.[109] At 60 months follow-up, subsequent revascularisation rates were significantly lower in participants receiving CABG plus OMT compared to OMT alone,[106] indicating 16 fewer subsequent revascularisation procedures per 100 patients compared to OMT alone (***Table 8***). However, there was considerable heterogeneity. Participants in the 2 trials were not homogeneous due to the BARI 2D trial enrolling patients with type 2 diabetes, which may have introduced heterogeneity. Certainty of evidence was moderate (***Figure 22***).

Figure 22 Risk ratio of subsequent revascularisation for CABG plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial.

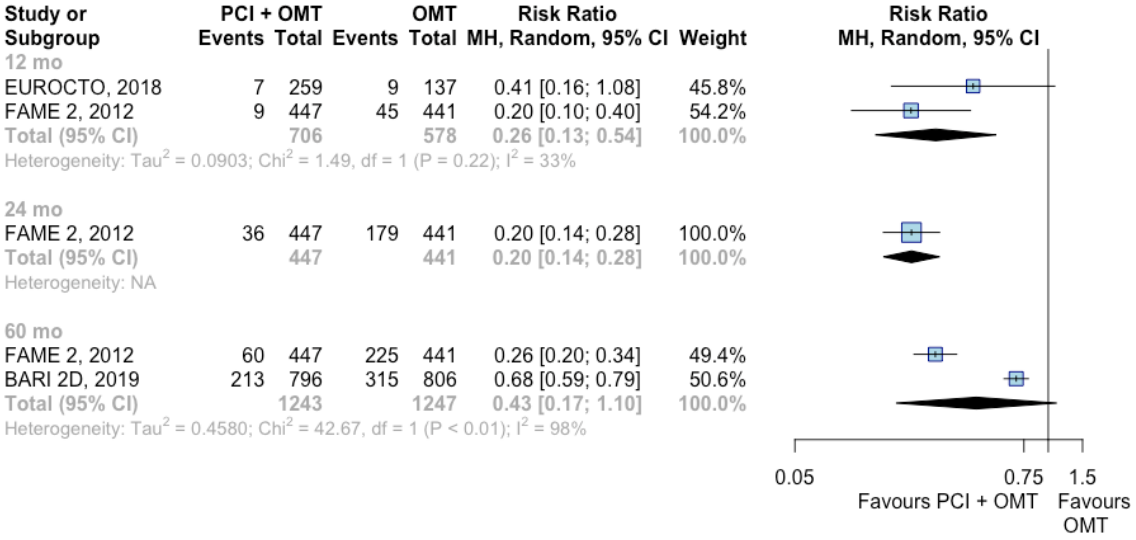
Notes

- OMT assumed to be equivalent between trial arms.

7.4.7.2 PCI plus OMT vs OMT alone

Subsequent revascularisation rates were significantly lower in participants receiving PCI plus OMT compared to OMT alone at both 12 months (heterogeneity low) and 24 months follow-up.[107,108,117,118] However, no significant differences were found at 60 months follow-up in 2 studies. Heterogeneity was considerable.[106] Participants in the 2 trials were not homogeneous due to all patients enrolled in the BARI 2D trial having type II diabetes, which may have produced the heterogeneity. Certainty of evidence was very low (***Figure 23***).

Figure 23 Risk ratio of subsequent revascularisation for PCI plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial**.**

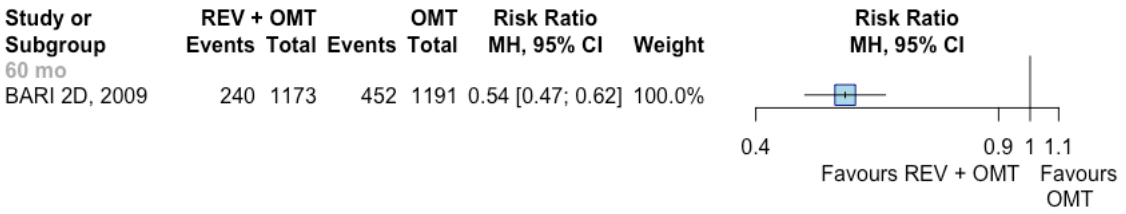
Notes

- OMT assumed to be equivalent between trial arms.

7.4.7.3 Revascularisation plus OMT vs OMT alone

Need for subsequent revascularisation was significantly lower in participants receiving revascularisation (i.e. CABG or PCI) plus OMT compared to OMT alone in 1 study at 60 months follow-up,[106] indicating 18 fewer subsequent revascularisation procedures per 100 patients compared with OMT alone (***Table 10***). Certainty of evidence was moderate (***Figure 24***).

Figure 24 Risk ratio of subsequent revascularisation for revascularisation plus OMT compared to OMT alone at 60 months (RCTs)



Abbreviations

CABG: coronary artery bypass graft; **CI:** confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI**: percutaneous coronary intervention; **RCT:** randomised control trial; **REV:** revascularisation.

Notes

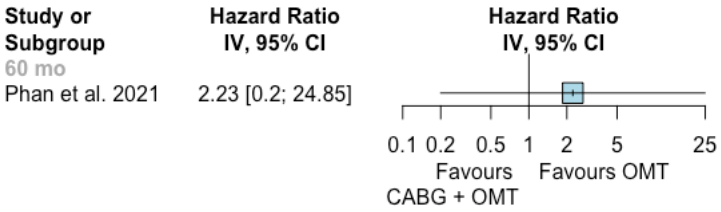
- OMT assumed to be equivalent between trial arms.
- Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

7.4.8 Subsequent revascularisation: NRSI evidence

7.4.8.1 CABG plus OMT vs OMT alone

One study reported that the HR for subsequent revascularisation was not significantly different between CABG plus OMT compared to OMT alone at 60 months follow-up (***Figure 25***).[124]

Figure 25 Hazard ratio of subsequent revascularisation for CABG plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **IV:** inverse variance; **mo:** months; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy.

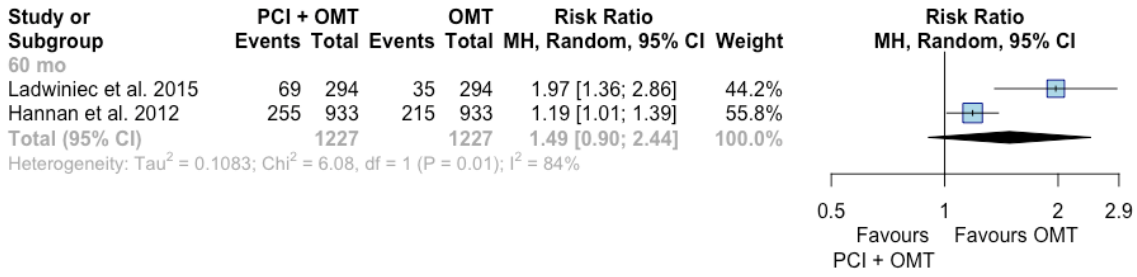
Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

7.4.8.2 PCI plus OMT vs OMT alone

The need for subsequent revascularisation was not significantly different between PCI plus OMT and OMT alone in 2 studies at 60 months follow-up. Heterogeneity was considerable (***Figure 26***).[122,123]

Figure 26 Risk ratio of subsequent revascularisation for PCI plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

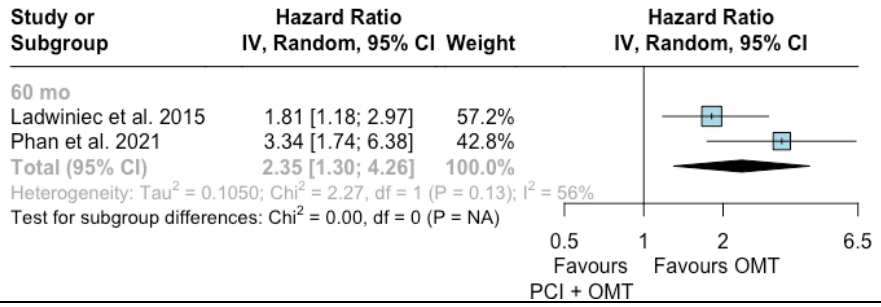
CI: confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

In 2 studies, the HR for subsequent revascularisation significantly favoured OMT alone compared to PCI plus OMT at 60 months follow-up, but heterogeneity was moderate (***Figure 27***).[122,123]

Figure 27 Hazard ratio of subsequent revascularisation following PCI plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CI: confidence interval; **IV:** inverse variance; **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

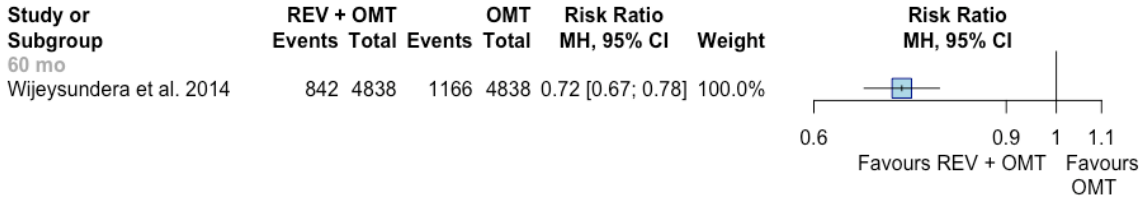
Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

7.4.8.3 Revascularisation plus OMT vs OMT alone

In 1 study, subsequent revascularisation rates were significantly lower in participants receiving revascularisation plus OMT compared to OMT alone at 60 months follow-up (***Figure 28***).[126]

Figure 28 Risk ratio of subsequent revascularisation for revascularisation plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **REV:** revascularisation.

Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

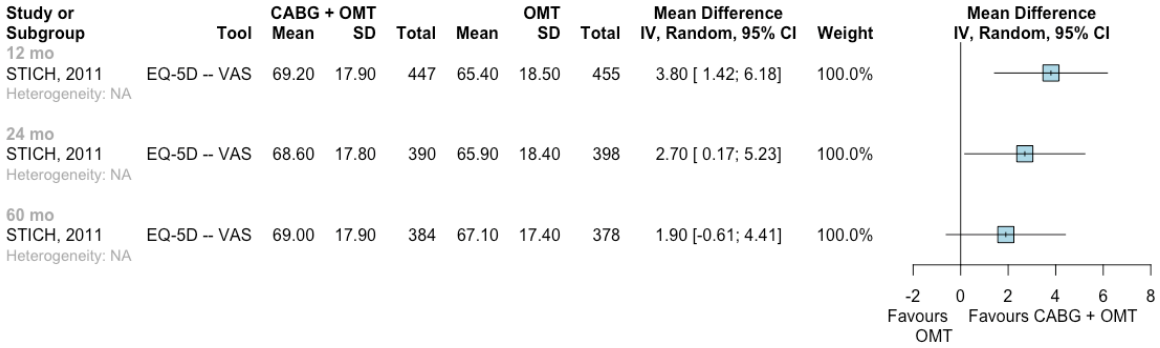
7.4.9 General HRQoL: RCT evidence

7.4.9.1 CABG plus OMT vs OMT alone

HRQoL scores (EQ-5D) were reported in 1 study at 12, 24 and 60 months.[115] At 12 months, participants receiving CABG plus OMT had significantly better quality of life (QoL) compared to OMT alone. Certainty of evidence was moderate. At 24 months, mean difference between treatment groups was smaller but

still favoured CABG plus OMT. At 60 months no significant differences were found between CABG plus OMT and OMT alone (***Figure 29***).

Figure 29 Mean difference of general HRQoL for CABG plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **EQ-5D–VAS:** European quality of life 5-dimension questionnaire – visual analogue scale; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **SD:** standard deviation; **RCT:** randomised control trial.

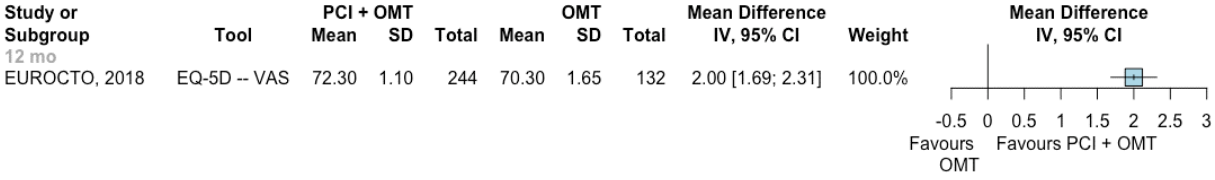
Notes

OMT assumed to be equivalent between trial arms.

7.4.9.2 PCI plus OMT vs OMT alone

In 1 study, participants receiving PCI plus OMT had significantly better EQ-5D HRQoL scores at 12 months follow-up. Certainty of evidence was low (***Figure 30***).[117]

Figure 30 Mean difference of general HRQoL for PCI plus OMT compared to OMT alone at 12 months (RCTs)



Abbreviations

CI: confidence interval; **EQ-5D–VAS:** European quality of life 5-dimension questionnaire – visual analogue scale; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **SD:** standard deviation; **RCT:** randomised control trial.

Notes

OMT assumed to be equivalent between trial arms.

7.4.9.3 Revascularisation plus OMT vs OMT alone

None of the included RCTs reported general HRQoL outcomes for the revascularisation plus OMT and OMT comparison.

7.4.10 General HRQoL: NRSI evidence

None of the included NRSIs reported usable general HRQoL data that were controlled for measured confounders.

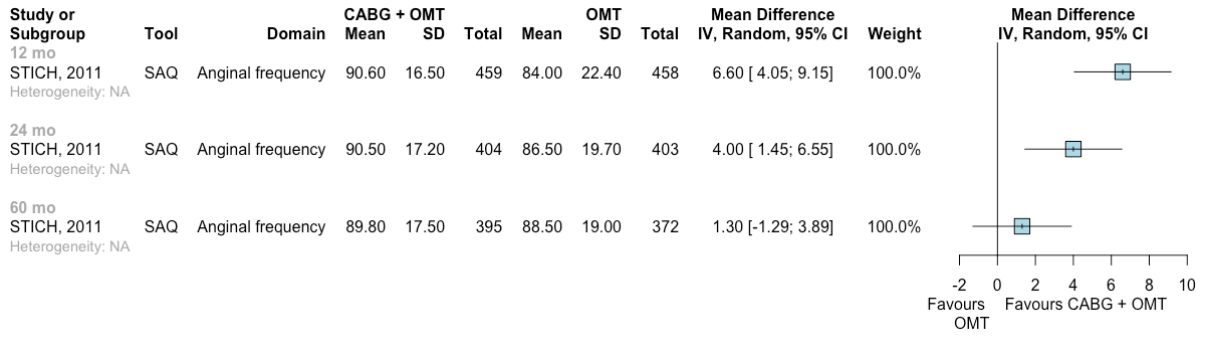
7.4.11 Cardiac-specific HRQoL: RCT evidence

7.4.11.1 SAQ domain: anginal frequency

7.4.11.1.1 CABG plus OMT vs OMT alone

Results from the SAQ were reported in 1 study at 12, 24 and 60 months.[111] At 12 months, participants receiving CABG plus OMT had significantly better angina HRQoL compared to OMT alone. At 24 months the mean difference between treatment groups was smaller but still favoured CABG plus OMT. At 60 months no significant differences were found between CABG plus OMT and OMT alone (***Figure 31***).

Figure 31 Mean difference of cardiac-specific HRQoL (using SAQ angina frequency) for CABG plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **RCT:** randomised control trial.

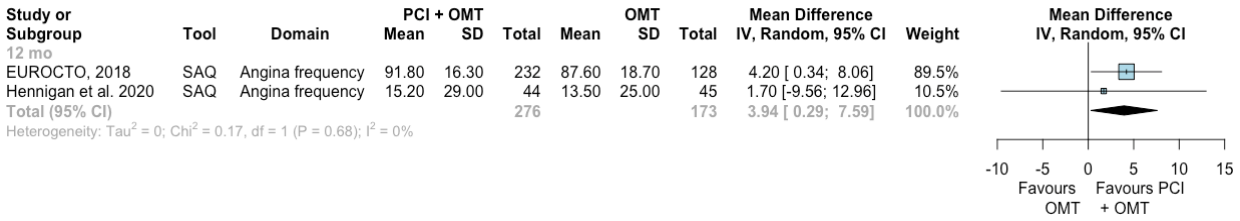
Notes

- OMT assumed to be equivalent between trial arms

7.4.11.1.2 PCI plus OMT vs OMT alone

In 2 studies, angina frequency scores at 12 months significantly favoured participants receiving PCI plus OMT compared to OMT alone.[110,117] Heterogeneity was low (***Figure 32***). Sensitivity analysis of imputed data and missing outcome data indicated no significant differences between groups.

Figure 32 Mean difference of cardiac-specific HRQoL (using SAQ angina frequency) for PCI plus OMT compared to OMT alone at 12 months (RCTs)



Abbreviations

CI: confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **RCT:** randomised control trial.

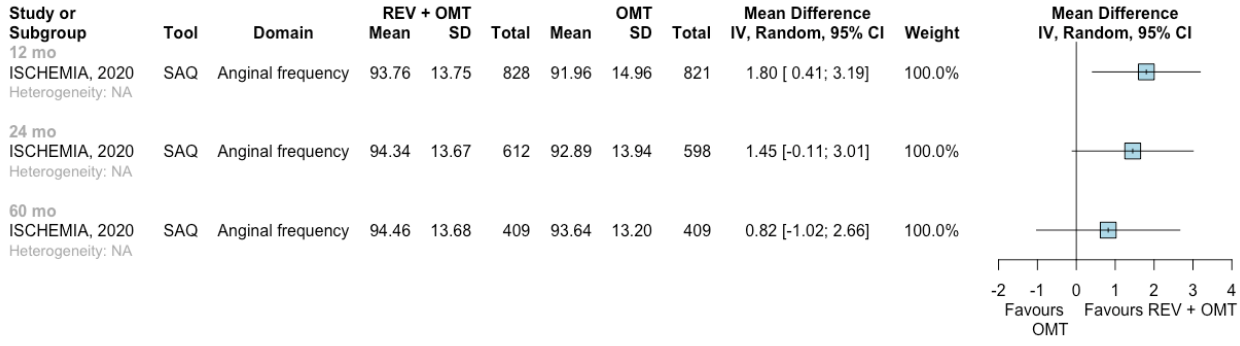
Notes

- OMT assumed to be equivalent between trial arms.
- Hennigan et al. 2020 reports SAQ domain scores as change from baseline, not as complete SAQ domain scores.

7.4.11.1.3 Revascularisation plus OMT vs OMT alone

Anginal frequency scores were reported in 1 study at 12, 24 and 60 months.[112] At 12 months, participants receiving revascularisation plus OMT had significantly better anginal scores compared to OMT alone. At 24 months the mean difference was not significantly different between interventions. Likewise, at 60 months no significant differences were found between revascularisation plus OMT and OMT alone (***Figure 33***).

Figure 33 Mean difference of cardiac-specific HRQoL (using SAQ angina frequency) for revascularisation plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CI: confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **REV:** revascularisation; **RCT:** randomised control trial.

Notes

- OMT assumed to be equivalent between trial arms.

7.4.11.2 SAQ domain: anginal stability

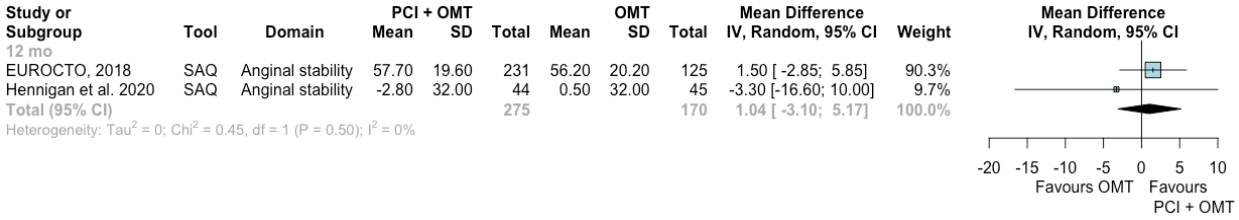
7.4.11.2.1 CABG plus OMT vs OMT alone

None of the included RCTs reported SAQ anginal stability outcomes for a comparison of CABG plus OMT and OMT.

7.4.11.2.2 PCI plus OMT vs OMT alone

Two studies reported SAQ scores at 12 months follow-up.[110,117] No significant differences were found between participants receiving PCI plus OMT and OMT alone. Heterogeneity was low (***Figure 34***).

Figure 34 Mean difference of cardiac-specific HRQoL (using SAQ anginal stability) for PCI plus OMT compared to OMT alone at 12 months (RCTs)



Abbreviations

CI: confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **RCT:** randomised control trial.

Notes

- OMT assumed to be equivalent between trial arms.
- Hennigan et al. 2020 reports SAQ domain scores as change from baseline, not as complete SAQ domain scores.

7.4.11.2.3 Revascularisation plus OMT vs OMT alone

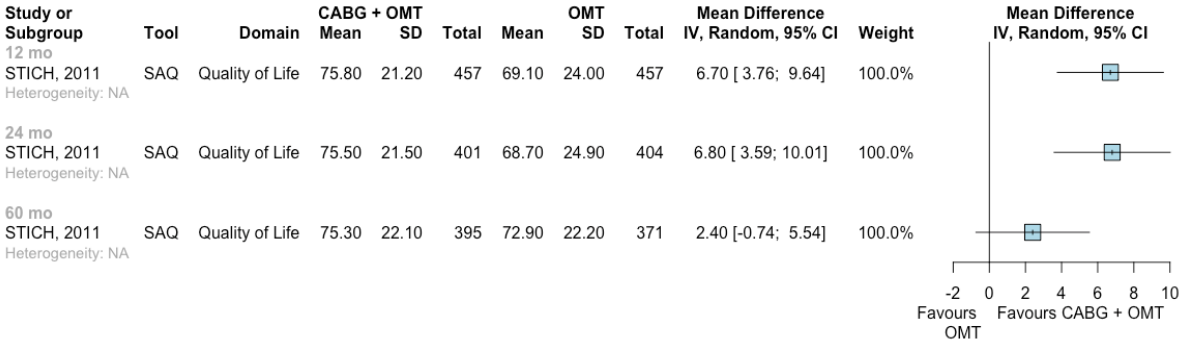
None of the included RCTs reported SAQ anginal stability outcomes for a comparison of revascularisation plus OMT and OMT.

7.4.11.3 SAQ domain: quality of life (QoL)

7.4.11.3.1 CABG plus OMT vs OMT alone

SAQ QoL scores were reported in 1 study at 12, 24 and 60 months.[111] At 12 months, participants receiving CABG plus OMT had significantly better QoL compared to OMT alone. At 24 months QoL still favoured participants receiving CABG plus OMT; however, at 60 months no significant differences in QoL were found between participants receiving CABG plus OMT and OMT alone (***Figure 35***).

Figure 35 Mean difference of cardiac-specific HRQoL (using SAQ QoL) for CABG plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **RCT:** randomised control trial, **QoL:** quality of life.

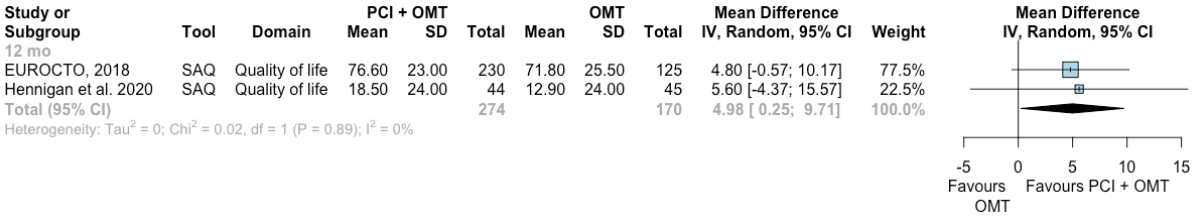
Notes

- OMT assumed to be equivalent between trial arms.

7.4.11.3.2 PCI plus OMT vs OMT alone

Two studies reported SAQ QoL scores at 12 months follow-up.[110,117] Participants receiving PCI plus OMT had significantly better QoL compared to participants receiving OMT alone. Heterogeneity was low (***Figure 36***). Sensitivity analysis of imputed data and missing outcome data revealed no significant differences between groups.

Figure 36 Mean difference of cardiac-specific HRQoL (using SAQ QoL) for PCI plus OMT compared to OMT alone at 12 months (RCTs)



Abbreviations

CI: confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **RCT:** randomised control trial, **QoL:** quality of life.

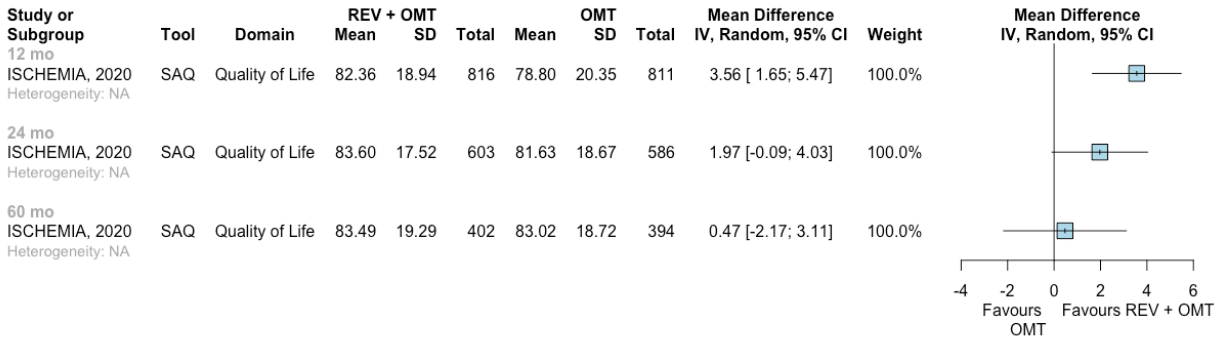
Notes

- OMT assumed to be equivalent between trial arms.
- Hennigan et al. 2020 reports SAQ domain scores as change from baseline, not as complete SAQ domain scores.

7.4.11.3.3 Revascularisation plus OMT vs OMT alone

SAQ scores for QoL were reported in 1 study at 12, 24 and 60 months.[112] At 12 months, participants receiving revascularisation plus OMT had significantly better QoL scores compared to OMT alone. At 24 months the mean difference was not significantly different between interventions. At 60 months no significant differences were found between revascularisation plus OMT and OMT alone (***Figure 37***).

Figure 37 Mean difference of cardiac-specific HRQoL (using SAQ QoL) for revascularisation plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CI: confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **REV:** revascularisation; **RCT:** randomised control trial, **QoL:** quality of life.

Notes

- OMT assumed to be equivalent between trial arms.

7.4.11.4 SAQ domain: physical limitation

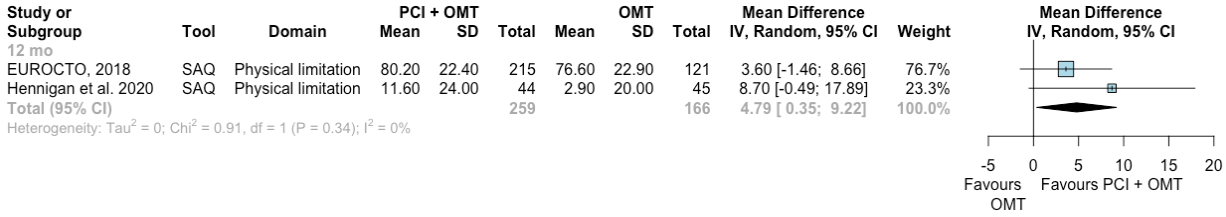
7.4.11.4.1 CABG plus OMT vs OMT alone

None of the included RCTs reported SAQ physical limitation outcomes for a comparison of CABG plus OMT and OMT alone.

7.4.11.4.2 PCI plus OMT vs OMT alone

Two studies reported SAQ scores for physical limitation at 12 months follow-up.[110,117] Results significantly favoured participants receiving PCI plus OMT compared to OMT alone. Heterogeneity was low (***Figure 38***). Sensitivity analysis with imputed data was not significantly different between groups.

Figure 38 Mean difference of cardiac-specific HRQoL (using SAQ physical limitation) for PCI plus OMT compared to OMT alone at 12 months (RCTs)



Abbreviations

CI: confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **RCT:** randomised control trial.

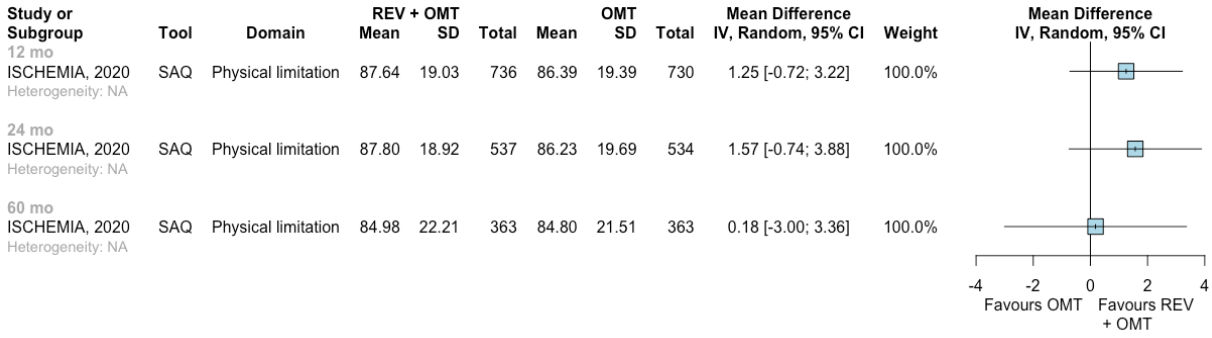
Notes

- OMT assumed to be equivalent between trial arms.
- Hennigan et al. 2020 reports SAQ domain scores as change from baseline, not as complete SAQ domain scores.

7.4.11.4.3 Revascularisation plus OMT vs OMT alone

Physical limitation scores were reported in 1 study at 12, 24 and 60 months.[112] At all timepoints no significant differences in physical limitation were found between participants receiving revascularisation plus OMT and OMT alone (***Figure 39***).

Figure 39 Mean difference of cardiac-specific HRQoL (using SAQ physical limitation) for revascularisation plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviation

CI: confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **REV:** revascularisation; **RCT:** randomised control trial.

Notes

- OMT assumed to be equivalent between trial arms.

7.4.11.5 SAQ domain: treatment satisfaction

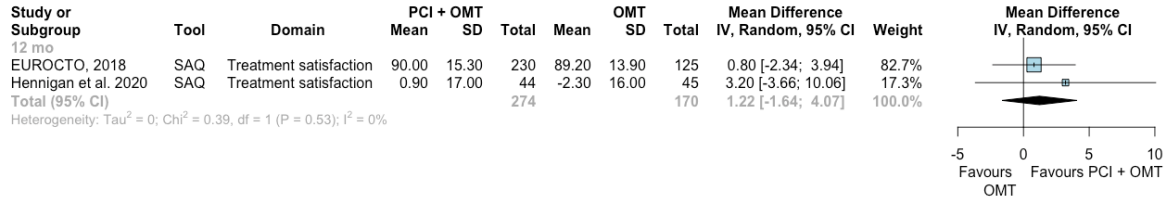
7.4.11.5.1 CABG plus OMT vs OMT alone

None of the included RCTs reported SAQ treatment satisfaction outcomes for a comparison of CABG plus OMT and OMT alone.

7.4.11.5.2 PCI plus OMT vs OMT alone

Two studies reported SAQ scores for treatment satisfaction at 12 months follow-up.[110,117] No significant differences were found between participants receiving PCI plus OMT and OMT alone. Heterogeneity was low (***Figure 40***).

Figure 40 Mean difference of cardiac-specific HRQoL (using SAQ treatment satisfaction) for PCI plus OMT compared to OMT alone at 12 months (RCTs)



Abbreviations

CI: confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **RCT:** randomised control trial.

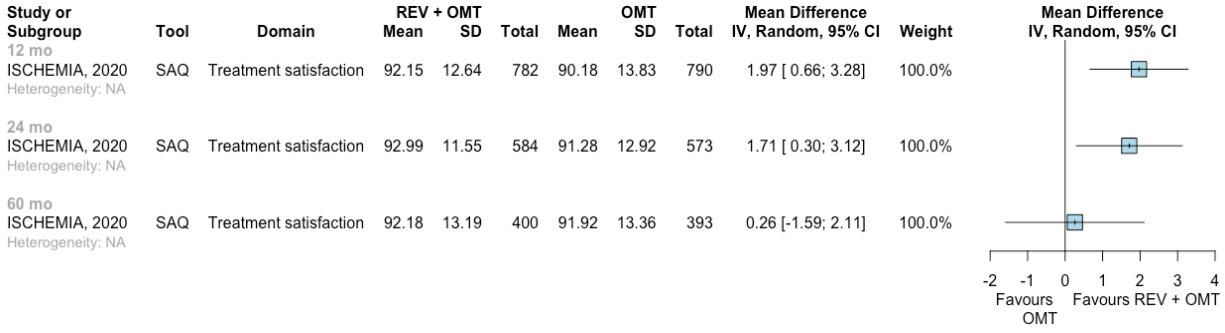
Notes

- OMT assumed to be equivalent between trial arms.
- Hennigan et al. 2020 reports SAQ domain scores as change from baseline, not as complete SAQ domain scores.

7.4.11.5.3 Revascularisation plus OMT vs OMT alone

SAQ treatment satisfaction scores were reported in 1 study at 12, 24 and 60 months.[112] At 12 months, participants receiving revascularisation plus OMT had significantly better treatment satisfaction compared to OMT alone. At 24 months treatment satisfaction significantly favoured participants receiving revascularisation plus OMT; however, by 60 months follow-up no significant differences were found between revascularisation plus OMT and OMT alone (***Figure 41***).

Figure 41 Mean difference of cardiac-specific HRQoL (using SAQ treatment satisfaction) for revascularisation plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviation

CI: confidence interval; **IV**: inverse variance method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial; **REV:** revascularisation; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation.

Notes

- OMT assumed to be equivalent between trial arms.

7.4.12 Cardiac-specific HRQoL: NRSI evidence

None of the included NRSIs reported usable cardiac-specific HRQoL data that were controlled for measured confounders.

7.4.13 Stent thrombosis: RCT evidence

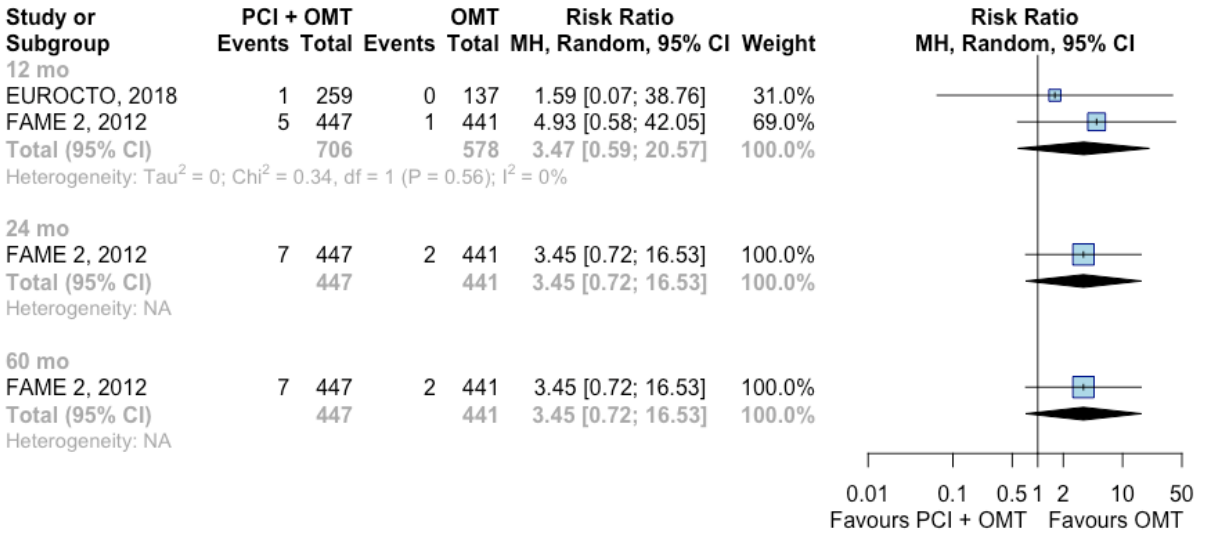
7.4.13.1 CABG plus OMT vs OMT alone

None of the included RCTs reported stent thrombosis outcomes for a comparison of CABG plus OMT and OMT alone.

7.4.13.2 PCI plus OMT vs OMT alone

The risk of stent thrombosis in participants receiving PCI plus OMT compared to OMT alone indicated no significant differences between groups at 12, 24 or 60 months follow-up. Heterogeneity was low (***Figure 42***).[107,108,117,118]

Figure 42 Risk ratio of stent thrombosis for PCI plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial.

Notes

- OMT assumed to be equivalent between trial arms.

7.4.13.3 Revascularisation plus OMT vs OMT alone

None of the included RCTs reported stent thrombosis outcomes for a comparison of revascularisation plus OMT and OMT alone.

7.4.14 Stent thrombosis: NRSI evidence

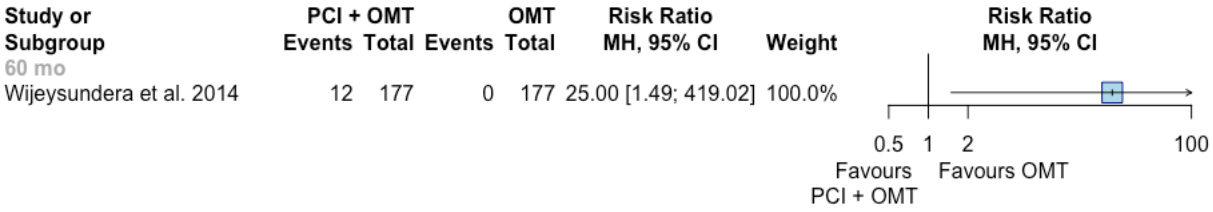
7.4.14.1 CABG plus OMT vs OMT alone

None of the included NRSIs that controlled for measured confounders, reported stent thrombosis outcomes for a comparison of CABG plus OMT and OMT alone.

7.4.14.2 PCI plus OMT vs OMT alone

In 1 study, the risk of stent thrombosis was significantly higher in participants receiving PCI plus OMT compared to OMT alone at 60 months follow-up (***Figure 43***).[126]

Figure 43 Risk ratio of stent thrombosis for PCI plus OMT compared to OMT alone at 60 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method **mo:** months; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

7.4.14.3 Revascularisation plus OMT vs OMT alone

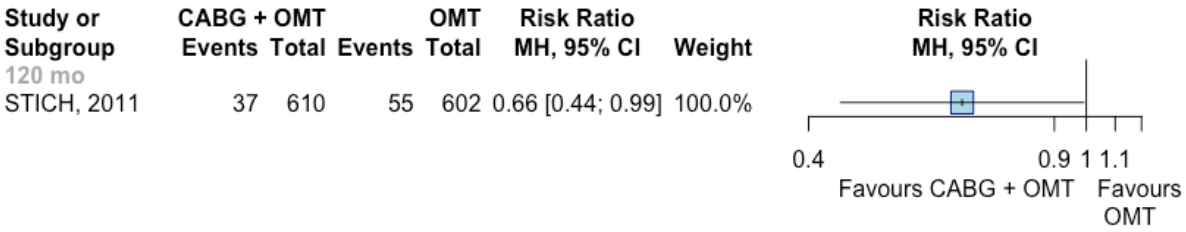
None of the included NRSIs that controlled for measured confounders reported stent thrombosis outcomes for a comparison of revascularisation plus OMT and OMT alone.

7.4.15 MI: RCT evidence

7.4.15.1 CABG plus OMT vs OMT alone

In 1 study, the risk of MI was significantly lower in participants receiving CABG plus OMT compared to OMT alone at 120 months follow-up, indicating 3 fewer MIs per 100 patients compared to OMT alone (***Table 8***). Certainty of the evidence was high (***Figure 44***).[116]

Figure 44 Risk ratio of MI for CABG plus OMT compared to OMT alone at 120 months (RCTs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **MI:** myocardial infarction; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial.

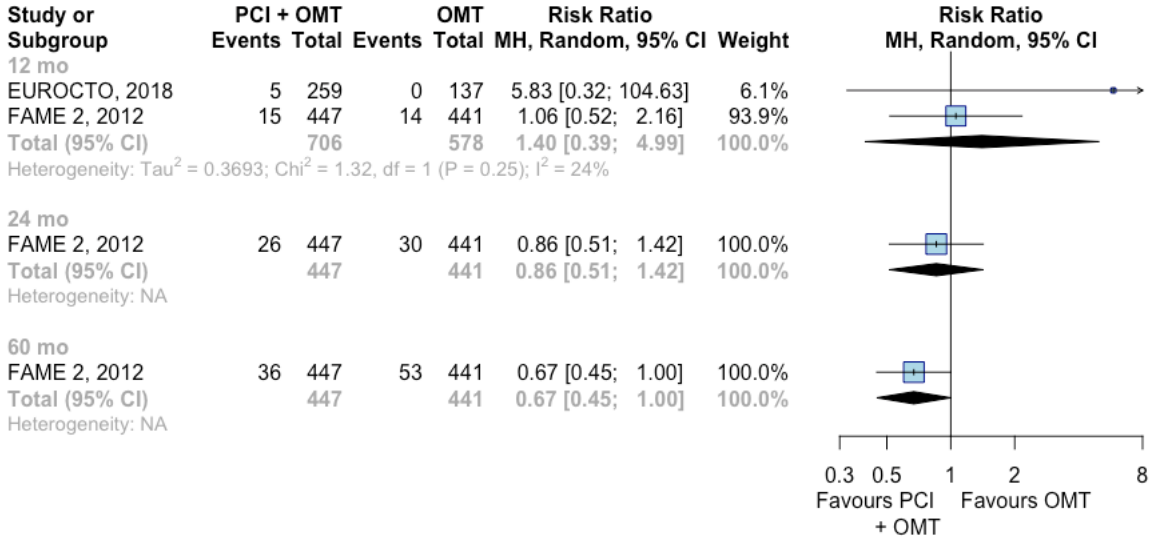
Notes

- OMT assumed to be equivalent between trial arms.

7.4.15.2 PCI plus OMT vs OMT alone

The risk of MI in 2 studies was not significantly different between PCI plus OMT and OMT alone at 12 months follow-up.[108,117] Heterogeneity was low. No significant differences between interventions were observed at 24 months follow-up[107] or at 60 months follow-up.[118] Certainty of evidence was high (***Figure 45***).

Figure 45 Risk ratio of MI for PCI plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **MI:** myocardial infarction; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial.

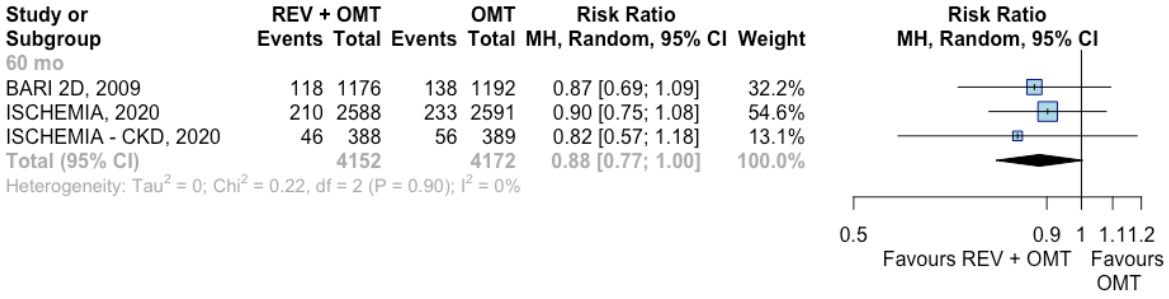
Notes

- OMT assumed to be equivalent between trial arms.

7.4.15.3 Revascularisation plus OMT vs OMT alone

In 3 studies, the risk of MI was not significantly different between revascularisation plus OMT and OMT alone at 60 months follow-up.[12,104,114] Heterogeneity was low and certainty of evidence was high (***Figure 46***).

Figure 46 Risk ratio of MI for revascularisation plus OMT compared to OMT alone at 60 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **MI:** myocardial infarction; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial**; REV:** revascularisation.

Notes

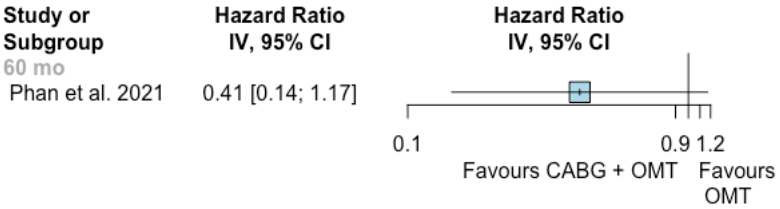
- OMT assumed to be equivalent between trial arms.
- Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

7.4.16 MI: NRSI evidence

7.4.16.1 CABG plus OMT vs OMT alone

In 1 study, no significant difference was observed for risk of MI in participants receiving CABG plus OMT compared to OMT alone at 60 months follow-up (***Figure 47***).[124]

Figure 47 Hazard ratio of MI for CABG plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **IV:** inverse variance; **MI:** myocardial infarction; **mo:** months; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy.

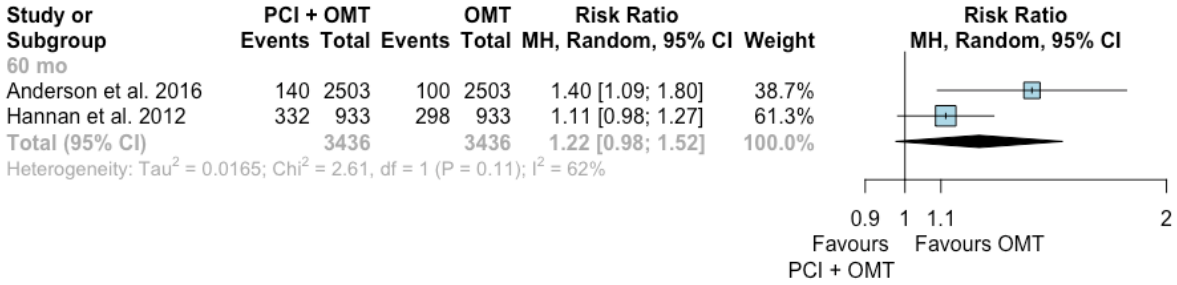
Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

7.4.16.2 PCI plus OMT vs OMT alone

In 2 studies, no significant difference was observed for risk of MI in participants receiving PCI plus OMT compared to OMT alone at 60 months follow-up.[119,122] Heterogeneity was substantial (***Figure 48***).

Figure 48 Risk ratio of MI for PCI plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **MI:** myocardial infarction; **mo:** months; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

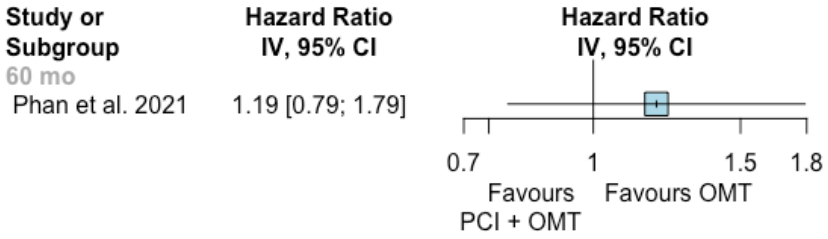
Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

7.4.16.3 Revascularisation plus OMT vs OMT alone

No significant difference was observed for MI between PCI plus OMT and OMT alone at 60 months follow-up (***Figure 49***).[124]

Figure 49 Hazard ratio of MI for PCI plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CI: confidence interval; **IV:** inverse variance; **MI:** myocardial infarction; **mo:** months; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

Notes

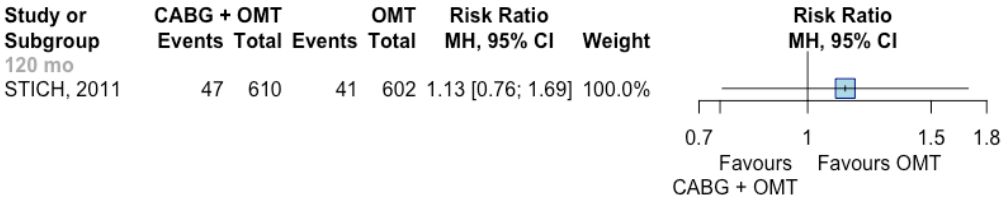
- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

7.4.17 Stroke: RCT evidence

7.4.17.1 CABG plus OMT vs OMT alone

No significant difference was observed for risk of stroke in participants receiving CABG plus OMT compared with OMT alone at 120 months follow-up. Certainty of evidence was moderate. (***Figure 50***).[116]

Figure 50 Risk ratio of stroke for CABG plus OMT compared to OMT alone at 120 months (RCTs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **OMT:** optimal medical therapy; **RCT:** randomised control trial.

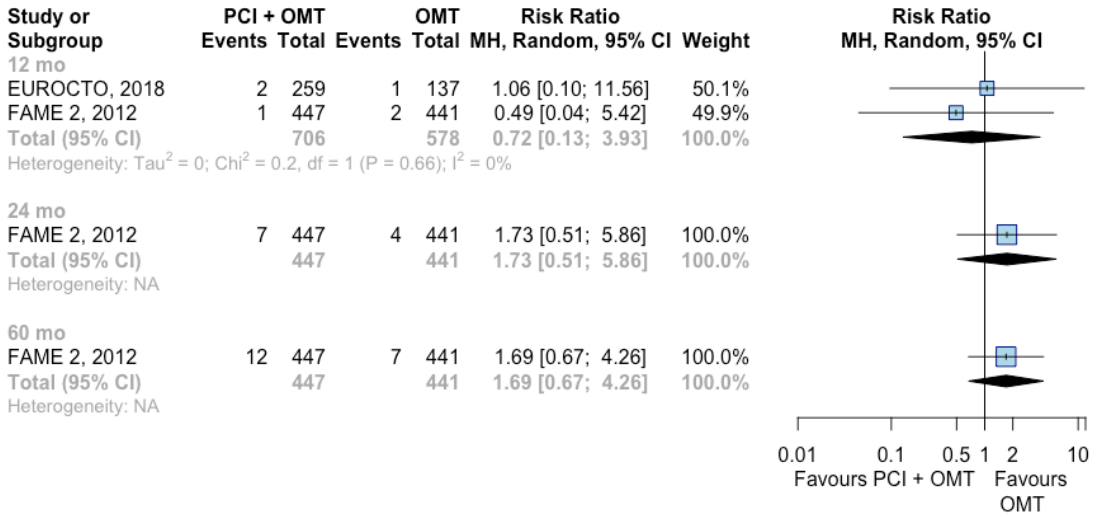
Notes

- OMT assumed to be equivalent between trial arms.

7.4.17.2 PCI plus OMT vs OMT alone

No significant differences were observed for risk of stroke in participants receiving PCI plus OMT compared to OMT alone at 12, 24 or 60 months follow-up. Heterogeneity was low. Certainty of evidence was low (***Figure 51***).[107,108,117,118]

Figure 51 Risk ratio of stroke for PCI plus OMT compared to OMT alone, 12–60 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial.

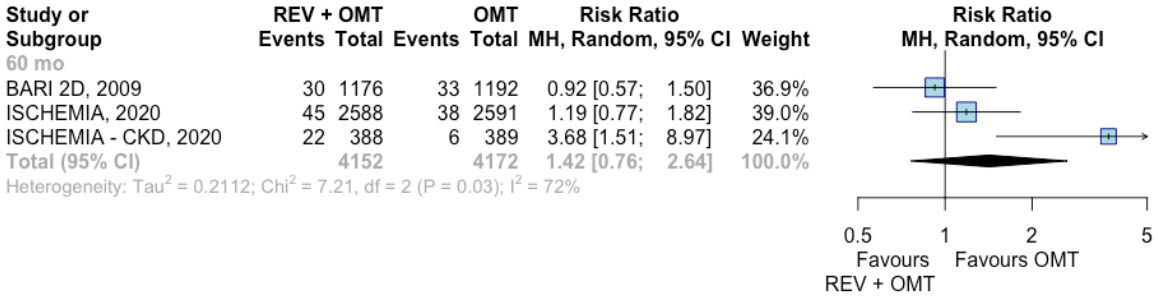
Notes

- OMT assumed to be equivalent between trial arms.

7.4.17.3 Revascularisation plus OMT vs OMT alone

In 3 studies, no significant difference was observed for risk of stroke in participants receiving revascularisation plus OMT compared to OMT alone at 60 months follow-up.[12,104,114] Heterogeneity was substantial and certainty of evidence was low. The ISCHEMIA–CKD trial significantly favoured OMT. This trial included participants with concurrent chronic kidney disease, which may explain the different direction in treatment effect and substantial heterogeneity (***Figure 52***).

Figure 52 Risk ratio of stroke for revascularisation plus OMT compared to OMT alone at 60 months (RCTs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **mo:** months; **OMT:** optimal medical therapy; **RCT:** randomised control trial; **REV:** revascularisation.

Notes

- OMT assumed to be equivalent between trial arms.
- Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

7.4.18 Stroke: NRSI evidence

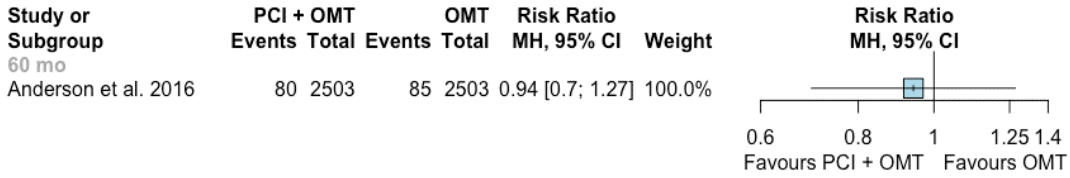
7.4.18.1 CABG plus OMT vs OMT alone

None of the included NRSIs that controlled for measured confounders reported stroke outcomes for a comparison of CABG plus OMT and OMT alone.

7.4.18.2 PCI plus OMT vs OMT alone

No significant difference was observed for risk of MI in participants receiving PCI plus OMT compared to OMT alone at 60 months follow-up (***Figure 53***).[119]

Figure 53 Risk ratio of MI for PCI plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method; **MI:** myocardial infarction; **mo:** months; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

7.4.18.3 Revascularisation plus OMT vs OMT alone

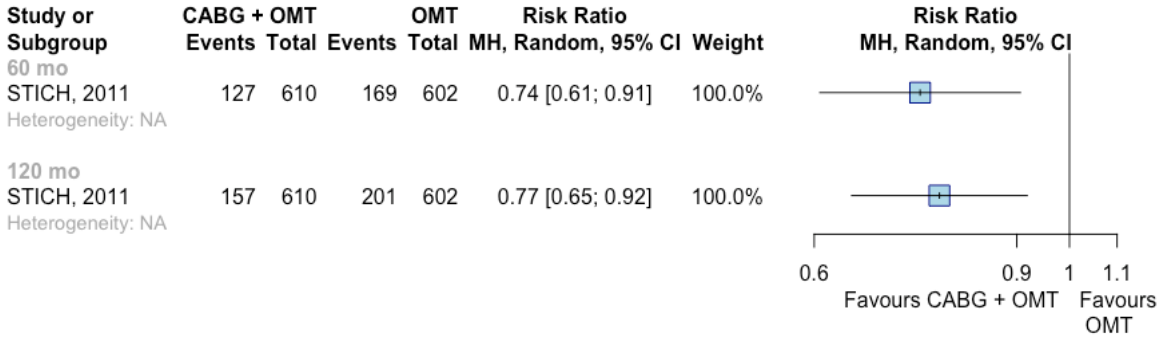
None of the included NRSIs that controlled for measured confounders reported stroke outcomes for a comparison of revascularisation plus OMT and OMT alone.

7.4.19 Hospitalisation due to HF: RCT evidence

7.4.19.1 CABG plus OMT vs OMT alone

Hospitalisation due to HF was reported in 1 study at 60 and 120 months.[116] At both timepoints hospitalisation due to HF was significantly lower in participants receiving CABG plus OMT compared to OMT alone (***Figure 54***).

Figure 54 Risk ratio of hospitalisation due to HF for CABG plus OMT compared to OMT alone, 60–120 months (RCTs)



Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval; **HF:** heart failure; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial.

Notes

- OMT assumed to be equivalent between trial arms.

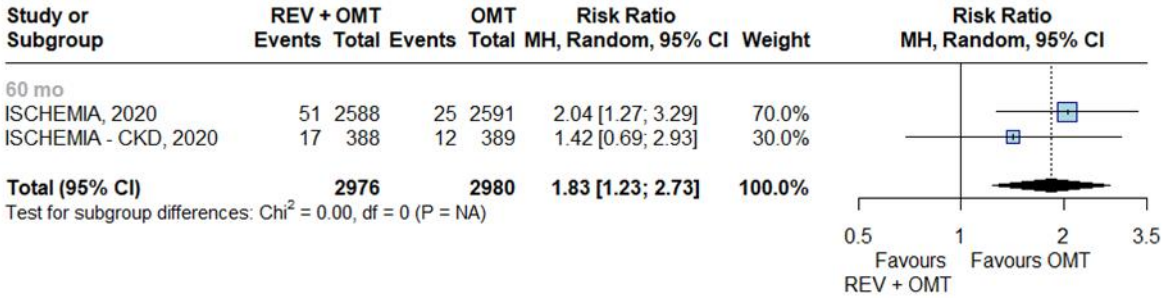
7.4.19.2 PCI plus OMT vs OMT alone

None of the included RCTs reported hospitalisation due to HF for a comparison of PCI plus OMT and OMT alone.

7.4.19.3 Revascularisation plus OMT vs OMT alone

Hospitalisation due to HF in participants with CAD was significantly lower in participants receiving OMT alone compared to revascularisation plus OMT at 60 months follow-up.[104,112] In participants with CAD complicated with chronic kidney disease, no significant difference was found between treatment groups (***Figure 55***).

Figure 55 Risk ratio of hospitalisation due to HF for revascularisation and OMT compared to OMT alone at 60 months (RCTs)



Abbreviations

CI: confidence interval; **HF:** heart failure; **MH:** Mantel-Haenszel method; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **RCT:** randomised control trial; **REV:** revascularisation.

Notes

- OMT assumed to be equivalent between trial arms.
- Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

7.4.20 Hospitalisation due to HF: NRSI evidence

None of the included NRSIs reported hospitalisation due to HF data that was controlled for measured confounders.

7.4.21 Target vessel revascularisation: RCT evidence

None of the included RCTs reported target vessel revascularisation (TVR).

7.4.22 Target vessel revascularisation: NRSI evidence

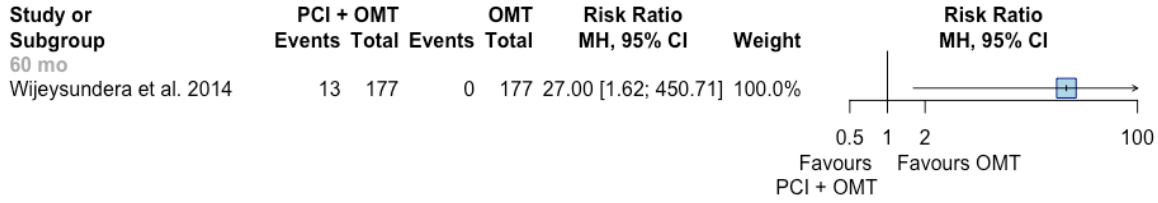
7.4.22.1 CABG plus OMT vs OMT alone

None of the included NRSIs that controlled for measured confounders reported TVR outcomes for a comparison of CABG plus OMT and OMT alone.

7.4.22.2 PCI plus OMT vs OMT alone

In 1 study, risk of TVR was significantly higher in participants receiving PCI plus OMT compared to OMT alone at 60 months follow-up (***Figure 56***).[126]

Figure 56 Risk ratio of target vessel revascularisation for PCI plus OMT compared to OMT alone at 60 months (NRSIs)



Abbreviations

CI: confidence interval; **MH:** Mantel-Haenszel method **mo:** months; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

Notes

- OMT assumed to be equivalent between trial arms.
- All included NRSIs controlled for measured confounders.

7.4.22.3 Revascularisation plus OMT vs OMT alone

None of the included NRSIs that controlled for measured confounders reported TVR outcomes for a comparison of revascularisation plus OMT and OMT alone.

7.5 GRADE Summary of Findings Tables

The overall strength of the evidence supporting the findings under investigation (clinical outcomes for surgical procedures CABG, PCI, revascularisation) are summarised below (***Table 8*** to ***Table 10***). Following the GRADE approach, a list of prioritised clinical outcomes is reported in the summary of findings (SoF).[96]

The included SoF tables only report the evidence from RCTs, not for NRSIs. This approach was chosen because some analyses reported heterogeneity in the reported results according to which outcome measure was reported (i.e. RR or HR) and this was not easily explained. Similarly, MACE is not reported in the GRADE tables due to differences in the definitions used in the included studies; however, individual components of MACE are reported separately. Also, many studies reporting HRs did not report event rates, so absolute risks associated with the interventions could not be calculated for the GRADE tables to provide context to the comparative result.

For all SoF tables (***Table 8*** to ***Table 10***), the risk (and associated 95% CI) in the intervention group is based on the assumed risk in the comparison group and the relative effect of the intervention (and associated 95% CI).[96]

The certainty of the evidence supporting an outcome, as scored according to the GRADE approach, is defined as follows:

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.[96]
- **Moderate certainty**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.[96]
- **Low certainty**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.[96]
- **Very low certainty**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.[96]

Table 8 Summary of RCT findings for CABG plus OMT compared to OMT alone at 60 months

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with OMT	Risk difference with CABG + OMT			
All-cause mortality	17 per 100	**3 fewer per 100** (7 fewer to 3 more)	**RR 0.83** (0.59 to 1.16)	763 (1 RCT)	⊕⊕◯◯ Low [a,b,c,d]
Hospitalisation	56 per 100	**9 fewer per 100** (14 fewer to 3 fewer)	**RR 0.84** (0.75 to 0.94)	1,212 (1 RCT)	⊕⊕⊕⊕ High [a,c]
Subsequent revascularisation	24 per 100	**16 fewer per 100** (21 fewer to 3 fewer)	**RR 0.33** (0.12 to 0.89)	1,974 (2 RCTs)	⊕⊕⊕◯ Moderate [a,b,c,e]
General HRQoL (measured using EQ-5D–VAS)	mean 67.10	MD **1.9 higher** (0.61 lower to 4.41 higher)	N/A	762 (1 RCT)	⊕⊕⊕◯ Moderate [c,d]
Stent thrombosis	N/A	N/A	N/A	N/A	N/A
MI‡	9 per 100	**3 fewer per 100** (5 fewer to 0 fewer)	**RR 0.66** (0.44 to 0.99)	1,212 (1 RCT)	⊕⊕⊕⊕ High [a,c]
Stroke‡	7 per 100	**1 more per 100** (2 fewer to 5 more)	**RR 1.13** (0.76 to 1.69)	1,212 (1 RCT)	⊕⊕⊕◯ Moderate [a,c,d]

Abbreviations:

CABG: coronary artery bypass; **CI**: confidence interval; **EQ-5D–VAS:** European quality of life 5-dimension questionnaire – visual analogue scale; **HRQoL:** health-related quality of life; **MD:** mean difference; **MI:** myocardial infarction; **mo:** months; **N/A:** not applicable; **NR:** not reported; **OMT:** optimal medical therapy; **RCT**: randomised controlled trial; **RR**: risk ratio.

Notes:

‡ Follow-up is 120 mo as this outcome at 60 mo was not reported.

[a] Low to moderate risk of selection bias due to participants being unblinded; however, this risk was unlikely to affect event outcomes.

[b] Downgraded due to risk of selection bias caused by poor randomisation.

[c] Trial(s) focus on subpopulation(s).

[d] Downgraded due to risk of imprecision, as included evidence is a single trial with moderately wide 95% CI.

[e] Inconsistency within evidence can be explained by both included trails focusing on subpopulations.

Table 9 Summary of RCT findings for PCI plus OMT compared to OMT alone at 60 months

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with OMT	Risk difference with PCI + OMT			
All-cause mortality	10 per 100	**1 more per 100** (1 fewer to 5 more)	**RR 1.13** (0.86 to 1.49)	2,073 (2 RCTs)	⊕⊕⊕◯ Moderate [a,b,c]
Hospitalisation ‡	6 per 100	**0 fewer per 100** (3 fewer to 7 more)	**RR 0.99** (0.43 to 2.28)	396 (1 RCT)	⊕⊕◯◯ Low [b,d]
Subsequent revascularisation	43 per 100	**25 fewer per 100** (36 fewer to 4 more)	**RR 0.43** (0.17 to 1.10)	2,490 (2 RCTs)	⊕◯◯◯ Very low [a,b,e,f]
General HRQoL (measured using EQ-5D–VAS)	mean 2.00	**MD 2 higher** (1.69 higher to 2.31 higher)	N/A	376 (1 RCT)	⊕⊕◯◯ Low [b,g]
Stent thrombosis	0 per 100	**1 more per 100** (0 fewer to 7 more)	**RR 3.45** (0.72 to 16.53)	888 (1 RCT)	⊕⊕◯◯ Low [b,d]
MI	12 per 100	**4 fewer per 100** (7 fewer to 0 fewer)	**RR 0.67** (0.45 to 1.00)	888 (1 RCT)	⊕⊕⊕⊕ High [b]
Stroke	2 per 100	**1 more per 100** (1 fewer to 5 more)	**RR 1.69** (0.67 to 4.26)	888 (1 RCT)	⊕⊕◯◯ Low [b,d]

Abbreviations:

CI: confidence interval; **EQ-5D–VAS:** European quality of life 5-dimension questionnaire – visual analogue scale; **HRQoL:** health-related quality of life; **MD:** mean difference; **MI:** myocardial infarction; **mo:** months; **N/A:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **RCT**: randomised controlled trial; **RR**: risk ratio.

Notes:

‡ Follow-up is 12 mo as this outcome at 60 mo was not reported.

[a] Downgraded due to risk of selection bias caused by poor randomisation.

[b] Low to moderate risk of selection bias due to participants being unblinded; however, this risk was unlikely to affect event outcomes.

[c] Trial(s) focus on subpopulation(s).

[d] Downgraded due to risk of imprecision, as included evidence is a single trial with moderately wide 95% CI.

[e] Downgraded due to risk of inconsistency, as 95% CI of included trials do not overlap.

[f] Downgraded due to risk of imprecision, as the summary measure has wide 95% CI and crosses the line of no effect.

[g] Downgraded due to significant uncertainty around how the outcome was measured.

Table 10 Summary of RCT findings for revascularisation plus OMT compared to OMT alone at 60 months

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with OMT	Risk difference with revascularisation + OMT			
All-cause mortality	18 per 100	**1 fewer per 100** (4 fewer to 3 more)	**RR 0.93** (0.78 to 1.17)	8,324 (3 RCTs)	⊕⊕⊕⊕ High [a]
Hospitalisation	2 per 100	**0 fewer per 100** (1 fewer to 4 more)	**RR 1.28** (0.50 to 3.32)	5,956 (2 RCTs)	⊕◯◯◯ Very low [a,b,c]
Subsequent revascularisation	38 per 100	**17 fewer per 100** (20 fewer to 14 fewer)	**RR 0.54** (0.47 to 0.62)	2,364 (1 RCT)	⊕⊕⊕◯ Moderate [a,d,e]
General HRQoL	NR	NR	N/A	NR	N/A
Stent thrombosis	NR	NR	NR	NR	N/A
MI	10 per 100	**1 fewer per 100** (2 fewer to 0 fewer)	**RR 0.88** (0.77 to 1.00)	8,324 (3 RCTs)	⊕⊕⊕⊕ High [a]
Stroke	2 per 100	**1 more per 100** (0 fewer to 3 more)	**RR 1.42** (0.76 to 2.64)	8,324 (3 RCTs)	⊕⊕◯◯ Low [a,b,c]

Abbreviations:

CI: confidence interval; **HRQoL:** health-related quality of life; **MD:** mean difference; **MI:** myocardial infarction; **mo:** months; **N/A:** not applicable; **NR:** not reported; **OMT:** optimal medical therapy; **REV**: revascularisation; **RCT**: randomised controlled trial; **RR**: risk ratio.

Notes:

[a] Low to moderate risk of selection bias due to participants being unblinded; however, this risk was unlikely to affect event outcomes.

[b] Downgraded due to risk of inconsistency, as the 95% CI of included trials only minimally overlap and point estimates are on differing sides of the line of no effect.

[c] Downgraded due to risk of imprecision, as the summary measure has wide 95% CI and crosses the line of no effect.

[d] Downgraded due to risk of selection bias caused by poor randomisation.

[e] Trial(s) focus on subpopulation(s).

8 Costs, cost-effectiveness and budget impact

Summary statement: costs, cost-effectiveness and budget impact

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A systematic review of the literature identified 7 cost-effectiveness studies and 4 costing studies assessing the cost or cost-effectiveness of PCI plus OMT or CABG plus OMT compared to OMT in patients with CCS. None were directly applicable to the HTA context, thus a de novo model was built.

A Markov model was developed to assess—from the perspective of the Swiss healthcare payer—the cost-effectiveness of revascularisation (i.e. PCI or CABG) plus OMT, PCI plus OMT and CABG plus OMT relative to OMT alone for the management of CCS. Costs associated with PCI and CABG, OMT, patient follow-up and the treatment of individual MACE outcomes were valued for the Swiss context. Baseline rates of MACE events were derived from RCTs, while baseline utility estimates were derived from an Austrian cohort of stable angina patients. Estimates of relative treatment effect on event rates and patient HRQoL were informed by the clinical evaluation.

The economic evidence demonstrated unfavourable outcomes (i.e. high ICERs or dominance) for all interventions when baseline risks of MACE events were derived from the ISCHEMIA RCT. For all comparisons, the relative effect of revascularisation with respect to all-cause mortality was a major driver of cost-effectiveness. Costs for inpatient PCI and CABG procedures, as well as the baseline annual mortality transition, were also important parameters. Economic outcomes improved when baseline event rates were sourced from more targeted population groups with higher baseline event risks, including patient cohorts with chronic kidney disease or LVEF ≤35%.

Under current policy conditions, CABG and PCI procedures for management of CCS were estimated to be responsible for anticipated costs of CHF59.7 million (sensitivity analysis: CHF53.7–65.6 million) and CHF146.1 million (sensitivity analysis: CHF132.5–159.8 million), respectively, in 2023. Considering observed trends in the use of revascularisation procedures over the period 2016 to 2019 (i.e. reducing utilisation of CABG, increasing utilisation of inpatient and outpatient PCI), anticipated CABG costs were projected to decrease to CHF51.2 million (sensitivity analysis: CHF46.0–56.3 million) in 2027, while anticipated PCI costs were projected to increase to CHF184.3 million (sensitivity analysis: CHF167.2–201.5 million). Scenario analyses using alternative data sources and/or assumptions for PCI procedure numbers reported costs for PCI of between CHF135.9 and 142.3 million in 2023, and between CHF114.1 and 156.2 million in 2027.

8.1 Methodology: costs, cost-effectiveness and budget impact

8.1.1 Study selection

The systematic literature searches outlined in ***Section 7.1*** were used to identify cost analyses, full economic evaluations (studies that value both costs and benefits of different treatments) and budget impact analyses assessing the cost, cost-effectiveness or budget impact of PCI plus OMT or CABG plus OMT compared to OMT in patients with CCS. As per the study selection criteria outlined in ***Table 2***, only studies performed in WHO Mortality Stratum A countries published on or after 1 January 2010 have been included, to capture data most applicable to current practice in Switzerland.

8.1.2 Data extraction, analysis and synthesis

Data pertaining to the following domains were extracted from both the cost and cost-effectiveness analyses: perspective, intervention and comparator, population characteristics, analysis methods, sources of evidence, results and additional comments (e.g. author conclusions). Data were extracted by one reviewer (DS) and checked by a second (MM). Extraction templates are available in ***Table 95***, ***Table 96*** and ***Table 97*** (***Appendix F***).

Results of the included cost and cost-effectiveness studies were synthesised narratively (***Section 8.2.2*** and ***Section 8.2.4***).

8.1.3 Assessment of evidence applicability

Each cost-effectiveness study was also assessed against the applicability checklist items outlined in the National Institute for Health and Care Excellence (NICE) appraisal checklist in order to appraise the study's applicability to the evaluation context.[152] The applicability appraisal template is available in ***Table 98*** (***Appendix F***). This checklist asks reviewers to consider the applicability of each study in terms of the population studied, interventions included, healthcare system of use, perspective of the analysis, discounting of future costs and outcomes, and the outcome measure used.

Studies were judged to be either directly applicable, partially applicable or not applicable, depending on whether all applicability criteria were met and, if not, whether this misalignment could change or was likely to change the conclusions about cost-effectiveness. Judgements were largely based upon the alignment of each study with the PICO criteria.

The applicability of the existing evidence to the evaluation context is described narratively (***Section 8.2.3***).

8.1.4 Methodology for the economic evaluation

The available published evidence was judged to be insufficient to answer the research questions posed in this HTA. Accordingly, we developed a de novo cost-effectiveness model to estimate the cost-effectiveness of CABG plus OMT vs OMT, PCI plus OMT vs OMT, and revascularisation (any) plus OMT vs OMT within a Swiss healthcare setting. The model was developed in TreeAge Pro (Version 2022 R2.0).[153] Key model assumptions are listed in ***Table 101***, ***Appendix F***. Model inputs are listed in ***Table 102***, ***Table 103***, ***Table 104*** and ***Table 105***, ***Appendix F***.

8.1.4.1 Perspective

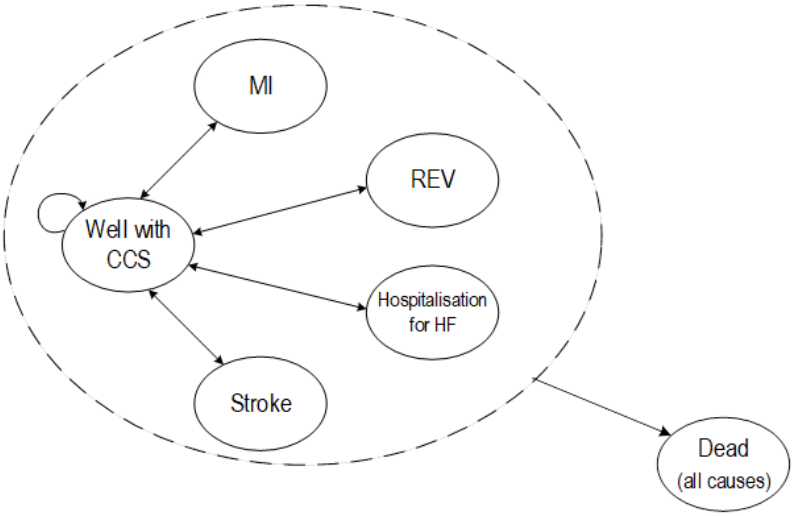
A Swiss healthcare payer perspective was adopted. Direct medical costs for services covered by mandatory health insurance (OKP) were included, irrespective of the actual payer (e.g. health insurer, other social insurer, government [federal government, cantons, communities] or patient). Non-medical and indirect costs (e.g. travel costs, informal care or productivity losses) were not considered. Costs are reported in Swiss francs (CHF) for a common costing year of 2022.

Effectiveness was measured in terms of the final health outcome of QALYs lived. Both costs and effects were discounted at 3.0% per annum.

8.1.4.2 Method used to generate the results

A state transition model was utilised to demonstrate the transition of patients through the main health states and events associated with CCS. Events of interest include the individual components of the MACE outcome defined in the PICO (***Table 1***, ***Section 5***), that is, MI, stroke, hospitalisation for HF, revascularisation and all-cause mortality. Health states included in the model reflect each of these events, as shown in ***Figure 57***.

Figure 57 State-transition diagram for the planned Markov model



Abbreviations:
CCS: chronic coronary syndrome; **HF**: heart failure; **MI**: myocardial infarction; **REV**: revascularisation.

An annual cycle length with half cycle correction was used in the model. The definition for CCS provided in the ***HTA Protocol*** specified CCS patients as those diagnosed with atherosclerotic coronary arteries without acute symptoms who have not experienced an acute event in the past 12 months.[1] This is reflected in the annual cycle length, with a return transition of patients from the MI or revascularisation state to the well-with-CCS state 1 year after the event.

Upon occurrence of a clinical event (non-fatal), patients transition to the relevant health state where they remain for one cycle (i.e. 1 year) before returning to the well-with-CCS state or transitioning to death (***Figure 57***). Transition to death is possible from any heath state.

The Markov model had no memory of what had occurred in earlier model cycles. It was assumed that all patients in the well-with-CCS state were at the same risk of future events, regardless of whether they had experienced a prior event. Therefore, any impacts that past events could have on future event risks were not captured.

Cohort expected value analysis was used to generate the results. Revascularisation plus OMT, PCI plus OMT and CABG plus OMT were compared against OMT alone in separate pairwise comparisons. Results were expressed as incremental cost per QALY gained.

8.1.4.3 Time horizon

The time horizon of an economic evaluation should be long enough to capture in full the differences in cost and effect of the options being compared.[154]

Results were analysed in a stepped fashion, before and after extrapolation. Two different time horizons were considered: one reflecting the length of longest follow-up, the other capturing the remaining lifetime of the model cohort. Length of longest follow-up was determined for each intervention separately and was informed by the longest timepoint for which clinical evidence was available. This was 5 years for both PCI and revascularisation, and 10 years for CABG. Beyond these timepoints, extrapolations of the clinical data were required. To capture the remaining lifetime of the model cohort, a time horizon of 36 years was used. The average age of patients included in the ISCHEMIA RCT and the western/central European cohort of the CLARIFY registry was 64 years (median) and 65.9 years (mean), respectively.[12,155]

For each outcome, any observed reductions in events risks were assumed to attenuate after trial follow-up.

8.1.4.4 Characterising uncertainty

Uncertainties in the base-case estimates were explored using one-way deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). One-way DSA was used to identify the key model

drivers of each pairwise comparison. The range over which each parameter was varied reflected 95% CI or ranges. Results were presented using tornado diagrams.

PSA was used to capture the joint uncertainty across model parameters, giving decision-makers information on the overall certainty of the economic outcomes. Distributions representing uncertainty around the mean estimate were imposed on model inputs. The choice of distribution depended on the information available and the nature of the input parameters. Parameter values were randomly sampled from their assigned distributions and the model was run repeatedly for each combination of parameter estimates. PSAs were run using 100,000 iterations. Results were presented as 95% confidence ellipses on the cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs).

8.1.4.5 Interpreting cost-effectiveness

There is no accepted willingness to pay (WTP) threshold in Switzerland. Using CEACs produced via PSAs, the probability of cost-effectiveness was expressed as a function of WTP.

8.1.4.6 Subgroup analyses

A secondary objective of the cost-effectiveness analysis was to explore whether cost-effectiveness of either PCI plus OMT or CABG plus OMT compared to OMT alone is affected by characteristics impacting patient risk and/or prior revascularisation.

Subgroups, defined *a priori* (see the ***Economic Analysis Plan***, available upon request) as patients with the following characteristics, were not analysed: hypertension, valvular heart disease, heart transplant, cancer, diabetes, obesity, advanced age (over 75 years), sex, LMCA stenosis >50%, refractory angina, prior revascularisation (vs naïve revascularisation).

Subgroup analyses were undertaken to explore cost-effectiveness under changing assumptions of target populations and associated baseline event rates (see ***Section 8.3.2.2*** for further detail). These analyses were informed by the available RCTs. The RCTs provided results for some patient groups excluded from the study informing the baseline transitions in the base case (i.e. the ISCHEMIA trial), those being: revascularisation plus OMT in patients with chronic kidney disease[104] and CABG plus OMT in patients with LVEF <35%.[115] These patients groups were considered in subgroup analyses. In addition, a subgroup analysis for PCI plus OMT in patients with high event risk based on invasive functional testing (i.e. FFR ≤0.8)[1] was also considered.

For the subgroup analysis, the following parameters were changed: annual transition probabilities for each MACE event; start age of the model cohort.

8.1.4.7 Scenario analyses

Scenario analyses in which only statistically significant RRs were included in the model were conducted for each of the base case models. For PCI, the only MACE outcome upon which statistically significant impact was observed was revascularisation (up to 2 years; ***Figure 23***). For revascularisation, a statistically significant effect in favour of the intervention was observed for subsequent revascularisation (up to 5 years; ***Figure 24***), while a significant effect in favour of the comparator was observed for hospitalisation due to HF (up to 5 years; ***Figure 55***).For CABG, statistically significant impacts for all MACE outcomes except for stroke were observed (up to 10 years for all-cause mortality, MI and hospitalisation for HF; up to 5 years for revascularisation; ***Figure 9***, ***Figure 22***, ***Figure 44*** and ***Figure 54***). For all MACE outcomes for which no statistically significant effect of invasive intervention was reported, the RR input in the model was set to 1.

Scenario analyses were also undertaken in which only statistically significant RRs were included in the model and in which significant treatment benefits still present at last observed follow-up were extrapolated under the assumption of continuing effect. These scenarios applied to the revascularisation and CABG analyses only.

Finally, scenario analyses on the assumed discount rate of 3% p.a. for costs and effects were undertaken, using alternative rates of 0% and 6% p.a.

8.1.4.7.1 Additional scenario analyses for the PCI plus OMT vs OMT comparison

Discussion with a clinical expert emphasised that the main outcomes to look for when treating CCS are symptom control and HRQoL improvement. Clinical evidence on the change in HRQoL after revascularisation was available up to 60 months for revascularisation or CABG but was limited to 12 months follow-up for PCI.

The approach taken in the extrapolation of treatment effects in the base case was to assume that treatment effects attenuated after the last timepoint for which follow-up data were available. Scenario analyses were undertaken to explore the impact of changing the extrapolation approach for change in HRQoL after PCI. In the scenario analyses, it was alternatively assumed that any changes in HRQoL reported at 12 months would persist for 24 or 60 months before attenuating.

Additional scenarios were also undertaken combining this alternative extrapolation approach for change in HRQoL after PCI with alternative assumptions with respect to MACE outcomes (i.e. setting the RR for mortality to 1 for the entire model horizon or including only statistically significant RR estimates).

8.1.5 Methodology for the budget impact analysis

8.1.5.1 Patient numbers

Annual numbers of Swiss CCS patients currently and historically undergoing PCI and CABG procedures were estimated using data from the TARMED (Tarifpool © SASIS AG) and MedStat databases.[156] Annual statistics published by the Swiss Working Group Interventional Cardiology were also considered. Estimated patient numbers were extrapolated to project the number of revascularisation procedures for CCS over 5 years under current policy conditions.

Revascularisation procedures may be billed using either TARMED tariffs (PCI: 17.1110 to 17.1190) or Swiss diagnosis-related groups (DRGs) (CABG: F06A, F06B, F06C, F06D; PCI: F24A, F24B, F24C, F24D, F24E, F24F). These codes are applicable for indications other than CCS (i.e. ACS).

For inpatient procedures billed using the Swiss DRG system, hospitalisation episodes associated with a diagnosis of chronic ischaemic heart disease (ICD-10 code: I25 [chronic ischaemic heart disease] and I20.1 to 120.9 [angina pectoris])[157] and a relevant procedure code (CHOP code: 36.0 [removal of coronary artery obstruction and placement of stent(s)], 36.1 [bypass anastomosis for myocardial revascularisation] and codes 00.66.29, 00.66.21, 00.4C12 and 00.4C11 [PTCA with drug-eluting balloons])[158] registered within the MedStat database were identified (see ***Table 99*** and ***Table 100***, ***Appendix F***).

For outpatient PCI procedures billed under TARMED, positions 17.1110 to 17.1190 relate to percutaneous transluminal coronary angioplasty (PTCA) procedures, with position 17.1110 being billed for 'PTCA for coronary stenoses or coronary occlusions (first dilated vascular segment)'. Claims data associated with this TARMED position were assumed to reflect the number of outpatient PCIs. Diagnosis-related information is unavailable in TARMED, therefore an assumption was made about the proportion of claims for CCS patients based on the proportion observed in the DRG data (see ***Section 8.3.5.2***).

8.1.5.2 Budget impact analysis

Anticipated costs of revascularisation procedures (PCI or CABG) over the period 2023 to 2027 were estimated.

Numbers of CABG and PCI procedures performed annually were estimated using a market share approach based on MedStat and TARMED (Tarifpool © SASIS AG) utilisation data,[156] taking into account that only a percentage of the total figures would reflect revascularisation procedures for patients with CCS.

The base scenario estimated expected payer costs under current policy conditions. The financial implications of potential policy changes (i.e. restriction of or disinvestment from revascularisation procedures for CCS) were not modelled.

8.2 Results of the literature review

8.2.1 Search results

A PRISMA flowchart summarising the overall systematic literature search is available in ***Figure 1*** (***Section 7.2.1***). In brief, 7 cost-effectiveness studies and 4 costing studies were identified.

Summary tables for the identified cost-effectiveness and costing studies are provided in ***Table 11*** and ***Table 12***, respectively. The narrative synthesis follows (***Section 8.2.2*** and ***Section 8.2.4***). Full extraction templates are available in ***Table 95***, ***Table 96*** and ***Table 97*** (***Appendix F***).

Table 11 Summary of findings of included cost-effectiveness studies

Study; perspective	Population characteristics	Analysis methods	Author's conclusion
CABG + OMT vs OMT			
Chew, 2022[128] US healthcare system	Patients age ≥18 years with LVEF ≤35% and CAD amenable to CABG.	**Evaluation type**: model based. **Model type**: individual patient-level state transition simulation model with 2 health states (alive and dead). **Time horizon**: lifetime. **Outcome measure:** incremental cost per QALY gained. **Discount rate**: 3% p.a. for costs and outcomes. **Cycle length**: 1 month.	In patients with ischemic cardiomyopathy and a reduced LVEF, CABG is economically attractive relative to OMT alone at current WTP thresholds in the US.
PCI + OMT vs OMT			
Fearon, 2018[129] US healthcare system	Patients age ≥21 years with stable angina, single- or multi-vessel CAD, ≥1 stenosis in a major coronary artery with FFR ≤0.8 and LVEF ≥30%.	**Evaluation type**: trial based. **Time horizon**: 3 years. **Outcome measure:** QALY. **Discount rate**: none.	3-year results from the FAME 2 trial show that, in patients with CCS and at least 1 lesion with an abnormal FFR, PCI improves outcomes and is economically attractive compared with OMT alone.
Fearon, 2013[130] US healthcare system	Patients age ≥21 years with stable angina, single- or multi-vessel CAD, ≥1 stenosis in a major coronary artery with FFR ≤0.8 and LVEF ≥30%.	**Evaluation type**: trial based. **Time horizon**: multiple used depending on assumption for extrapolation of HRQoL benefit (up to 4 years; 3 years in the base case). NB: Difference in cost at 12 months is assumed to remain constant over the extrapolation period. **Outcome measure:** incremental cost per QALY gained. **Discount rate**: none.	In patients with symptomatic CCS, PCI in the setting of an abnormal FFR improves angina and HRQoL and appears to be economically attractive compared with OMT if one assumes that the benefit of PCI lasts longer than 1 year.

Study; perspective	Population characteristics	Analysis methods	Author's conclusion
Gada, 2012[131] US healthcare provider	Patients with CTO, chronic stable angina, CCS class III–IV.	**Evaluation type**: model based. **Model type**: Markov model. Events/states: peri-procedural events (arterial complications, MI, tamponade, CABG, CVA, death); post-PCI states (successful or unsuccessful); post-PCI events (MI, TVR [PCI or CABG], stent thrombosis or death). Patients on OMT had annual rates of CABG and death. **Time horizon**: 5 years. **Outcome measure:** incremental cost per QALY gained. **Discount rate**: 5% p.a. for costs and outcomes. **Cycle length**: 1 year.	The results of this decision-analytic model suggest that CTO-PCI is cost effective in a patient population with severe symptoms.
Gorenoi, 2011[132] German restricted societal.	Patients with stable angina.	**Evaluation type**: model based. **Model type**: simplified linear simulation model. **Time horizon**: 5 years. **Outcome measure**: incremental cost per patient with avoided AP attacks. **NB**: It was assumed that the cost difference was caused exclusively by a difference in the rate of revascularisation with PCI (primary and during follow-up).	Although there are no recognised WTP values against which to assess the cost-effectiveness of an intervention in relation to avoided angina episodes, the authors conclude that PCI cannot be considered cost effective, citing a WTP of US$8,000 to avoid repeat revascularisation.
Kodera, 2019[134] (angina cohort) Japanese healthcare system	Patients with symptomatic angina and significant stenosis confirmed on FFR.	**Evaluation type**: model based. **Model type**: Markov model with 8 health states (AP, acute MI, old MI, new PCI, post PCI, new stroke, old stroke, and dead). **Time horizon**: 30 years. **Outcome measure:** incremental cost per QALY gained. **Discount rate**: 2% p.a. for costs and outcomes. **Cycle length**: 1 month.	FFR-guided PCI for symptomatic angina could be cost effective compared with OMT alone.
Wijeysundera, 2013[137] Canadian healthcare payer.	Patients with CCS with symptoms sufficient to warrant coronary angiography and with angiographic confirmation of hemodynamically significant coronary stenoses.	**Evaluation type**: model based. **Model type**: Markov model with 4 subtrees: (1) OMT only; (2) PCI; (3) MI; (4) CABG (if need for revascularisation after 3 previous PCIs only). **Time horizon**: lifetime. **Outcome measure:** incremental cost per QALY gained. **Discount rate**: 5% p.a. for costs and outcomes. **Cycle length**: 1 month.	This evaluation of PCI vs OMT found that an initial strategy of PCI-BMS was cost-effective. NB: Estimates for DES were predominantly from first generation stents. Calculated pairwise ICER suggests PCI-DES may also be cost effective relative to OMT at the WTP threshold of Canadian $50,000 per QALY.[A]

Abbreviations:

AP: angina pectoris; **BMS**: bare metal stent; **CABG**: coronary artery bypass graft; **CAD**: coronary artery disease; **CCS**: Canadian Cardiovascular Society; **CTO**: chronic total occlusion; **CVA**: cerebrovascular accident; **DES**: drug-eluting stent; **FAME**: Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; **FFR**: fractional flow reserve; **HRQoL:** health-related quality of life; **LVEF**: left ventricular ejection fraction; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **p.a**.: per annum; **PCI**: percutaneous coronary intervention; **QALY**: quality-adjusted life year; **TVR**: target vessel revascularisation; **US**: United States; **WTP**: willingness-to-pay.

Notes:

A: Calculated during this HTA based on reported expected costs and expected QALYs.

Table 12 Summary of findings of included cost analyses

Study; perspective	Population characteristics	Analysis methods	Author's conclusion
Caruba, 2015[127] French healthcare payer.	Patients age 50–70 years with CCS (i.e. no acute coronary syndrome or MI in the last 24 hours).	**Evaluation type**: Modelling study. **Time horizon**: 1 year. **Method/data source(s)**: probabilities of a patient being in 1 of 6 clinical scenarios after 1 year, according to the initial treatment used, were derived via a literature search (or informed by expert opinion). Resource use was modelled based on guidelines and clinical studies or expert opinion. Unit costs were assigned based on the costs to French statutory health insurance.	OMT appears to be the least costly option over 1 year. If reasonable from a clinical point of view, OMT might achieve appreciable savings in health expenditures compared with invasive treatments.
Kang, 2016[133] Canadian healthcare payer	Patients who underwent angiography for the indication of CCS (Oct 2008–Sept 2011) and who had obstructive coronary stenosis. OMT: n=15,138; revascularisation: n=23,988 (PCI: n=15,601; CABG: n=8,387).	**Evaluation type**: retrospective observational study. **Time horizon**: 1 year. **Method/data source(s)**: the primary outcome was the total cumulative cost per patient in the 1 year following the index angiography. Cost data were sourced from administrative databases in Ontario, Canada.	In this study, the major driver for 1-year costs was revascularisation. The decision to pursue a revascularisation strategy has a substantial impact on healthcare resources. Use of a short time horizon may bias results against CABG, because it is associated with fewer revascularisations in the long term.
McCreanor, 2019[135] Australian healthcare payer (limited to drug costs)	Patients with CAD (for OMT group, self-reported; for PCI or CABG group; with history of a relevant MBS procedure). OMT: n=609; PCI: n=92; CABG: n=39.	**Evaluation type**: prospective observational study. **Time horizon**: 1 year. **Method/data source(s)**: Australian administrative data (i.e. PBS data for PBS-listed pharmaceuticals used in the treatment of CAD) were extracted for 1 full year. These data were used to calculate an annual cost per patient.	A common argument for PCI in CCS is that it reduces the burden of medical therapy, particularly the need for symptom relief medications. However, this study found that PCI did not affect the costs or use of drugs used for angina relief. Further, the study showed that DAPT may frequently be continued for longer than recommended by the guidelines.
Stenvall, 2017[136] Finnish secondary healthcare provider (drug costs not included)	Stable patients entering elective coronary angiography (Nov 2002–Mar 2003) in whom CAD was confirmed. OMT: n=105; PCI =94; CABG: n=101.	**Evaluation type**: prospective observational study. **Time horizon**: 8 years. **Method/data source(s)**: data concerning costs and utilisation of secondary care services during the years 2002–2011 for 296 patients living in the immediate catchment area of the hospital were obtained from the administrative database of the hospital.	The 8-year mean secondary care costs of CABG were over 2-fold and almost 4-fold higher than PCI + OMT, respectively, even after adjustment for baseline characteristics.

Abbreviations:

CABG: coronary artery bypass graft; **CAD**: coronary artery disease; **DAPT**: dual antiplatelet therapy; **MBS**: Medicare Benefits Schedule (Australia); MI: myocardial infarction; **OMT**: optimal medical therapy; **PBS**: Pharmaceutical Benefits Scheme (Australia); **PCI**: percutaneous coronary intervention.

8.2.2 Findings: cost-effectiveness

8.2.2.1 CABG plus OMT vs OMT

One economic evaluation of the cost-effectiveness of CABG plus OMT vs OMT was identified (see ***Table 11*** and ***Table 95***, ***Appendix F***).[128] This study assessed the cost-effectiveness of CABG in patients with reduced left ventricular function (LVEF <35%) using patient-level clinical outcome and resource-use data from the Surgical Treatment for Ischemic Heart Failure (STICH) RCT.[115,116] A US healthcare system perspective was adopted for the analysis. Over the lifetime horizon of the evaluation, CABG plus OMT was associated with an incremental cost-effectiveness ratio (ICER) of US$63,989 per quality-adjusted life year (QALY) gained and showed 87% and 97% probabilities of being cost effective at the cited WTP thresholds (US$100,000 and $150,000, respectively). Subgroup analysis showed the cost-effectiveness of CABG to be greater in patients with LVEF ≤28% and in those with 3-vessel disease.

8.2.2.2 PCI plus OMT vs OMT

Six economic evaluations of the cost-effectiveness of PCI plus OMT vs OMT were identified: 2 trial-based analyses and 4 model-based analyses (see ***Table 11*** and ***Table 96***, ***Appendix F***).[129-132,134,137] The reported cost-effectiveness of PCI varied between the studies.

Three studies evaluated PCI in patients with at least one significant stenosis confirmed on fractional flow reserve (FFR).[129,130,134] All 3 studies utilised data from the FAME 2 (fractional flow reserve vs angiography for multivessel evaluation 2) RCT.[107,108] These studies found FFR-guided PCI to be cost effective compared to OMT alone from US and Japanese healthcare system perspectives over short- (3-year) and long-term (30-year) time horizons, respectively.[129,130,134] One of the US studies reported that FFR-guided PCI may be cost effective if one can assume that the benefit of PCI lasts longer than 1 year.[130] However, a Japanese model-based study reported an ICER well above the implicit WTP threshold of ¥5 million when HRQoL improvement with FFR-guided PCI was modelled to last for 2 years (ICER: ¥24.1 million per QALY).[134]

A model-based evaluation of PCI in patients with CTO and Canadian Cardiovascular Society class III or IV angina symptoms (i.e. more severe symptoms) found PCI to be cost effective over a 5-year time horizon from the perspective of the US healthcare provider.[131] The most important drivers of the cost-effectiveness outcome were the utility values of each of the major health states (i.e. post-successful PCI, post-unsuccessful PCI plus OMT states).

A model-based evaluation of PCI-DES (drug eluting stent/s) and PCI-BMS (bare mental stent/s) in patients with CCS and angiographic confirmation of significant coronary stenoses found an initial strategy of PCI-BMS to be cost effective from a Canadian third-party healthcare payer perspective over

a lifetime horizon.[137] Derivation of the ICER for the pairwise PCI-DES vs OMT comparison suggests PCI-DES may also be cost effective at the cited WTP threshold.

An economic evaluation performed as part of a German HTA report found that PCI could not be considered cost effective in patients with stable angina, comparing an ICER of €24,805 per patient-year-free-from-angina to a WTP of US$8,000 to avoid repeat revascularisation.[132,159] The evaluation assumed the cost difference was caused exclusively by a difference in the rate of PCI procedures (both initial and during a 5-year follow-up period).

8.2.3 Applicability: cost-effectiveness

8.2.3.1 CABG plus OMT vs OMT

The one included economic evaluation was only partially applicable, having been conducted in a US healthcare setting and within a subpopulation of CCS patients (i.e. those with LVEF ≤35%) (see ***Table 98***, ***Appendix F***).[128] Moreover, enrolment into the STICH RCT took place prior to 2010 and surgical techniques have advanced since then.

8.2.3.2 PCI plus OMT vs OMT

None of the identified studies were judged as fully applicable to the research question (see ***Table 98***, ***Appendix F***).

Four studies were judged as inapplicable. In one study, the intervention arm combined BMS and DES and it was unclear if OMT costs were included.[131] Another combined BMS and DES and did not use QALYs as the outcome measure.[132] In the third study, it was unclear if OMT costs were included in the intervention arm.[134] In the fourth study, data informing the DES arm pertained mainly to first generation DES, and the study compared PCI-DES with PCI-BMS and OMT via cost-effectiveness frontier analysis rather than providing a direct comparison between PCI-DES and OMT.[137] None of these 4 studies were conducted within a Swiss healthcare setting.

The remaining 2 studies were considered only partially applicable as they pertained to second generation DES, they were conducted in a US healthcare setting and were restricted to subpopulations of patients with at least one stenosis with FFR ≤80%.[129,130]

In addition to a partial lack of applicability in other domains, restrictions in translating the results of existing economic evidence to the Swiss context further limited the transferability of the partially applicable studies, all of which were conducted in the US healthcare setting, to the current HTA context.[128-130]

8.2.4 Findings: cost analyses

Four cost analyses were identified, including 3 observational studies using administrative data and 1 modelling study (see ***Table 12*** and ***Table 97***, ***Appendix F***).[127,133,135,136]

One study analysed the cost of medications used in the treatment of CCS over a 1-year time horizon from an Australian healthcare payer perspective.[135] This study found that, despite a belief that PCI for CCS reduces the burden of medical therapy, PCI did not affect the cost or use of drugs for angina relief.[135]

Another study, which estimated secondary care costs over an 8-year time horizon from a Finnish secondary healthcare payer perspective, found that after adjustment for baseline characteristics, secondary care costs of CABG were almost 4-fold higher than OMT, and PCI almost 2-fold higher.[136] Among the study cohort, patients with complex CAD (i.e. LMCA stenosis and multivessel disease) were more often treated with CABG.

One study, which estimated healthcare costs over a 1-year time horizon from a Canadian third-party payer perspective, found revascularisation to be a significant predictor of mean cost, regardless of the modality (PCI: cost ratio relative to OMT 1.27, 95% CI: 1.24 to 1.31; CABG: cost ratio 2.62, 95% CI 2.53 to 2.71).[133] The major driver of 1-year costs was revascularisation, highlighting that the decision to pursue revascularisation has a substantial impact on healthcare resource use. The authors suggest that the short time horizon may bias results against CABG, because the procedure is associated with fewer revascularisations in the long term.[133]

A study that modelled, over a 1-year time horizon, the occurrence of 6 clinical scenarios (clinical success, recurrence of symptoms without hospitalisation or revascularisation, MI, subsequent revascularisation without MI, death from non-cardiac cause, cardiac death) for 4 treatment strategies (CABG plus OMT, PCI-DES plus OMT, PCI-BMS plus OMT, OMT alone) to estimate the per-patient cost of each strategy, similarly found OMT to be the least costly option over 1 year.[127]

8.3 Results: costs, cost-effectiveness and budget impact

8.3.1 Findings: costs

Healthcare resources associated with PCI CABG, and OMT were identified, measured and valued. Costs from a healthcare payer perspective were estimated for the following: PCI and CABG procedures and associated hospital stays, OMT, follow-up and treatment of individual MACE outcomes of revascularisation, MI, stroke, and hospitalisation for HF.

Cost data for the year 2022 were sourced using resources such as Swiss DRG costs for inpatient services (Swiss DRG Version 11.0), the Spezialitätenliste for medicine costs, the Analysenliste for

laboratory costs and TARMED for outpatient medical services. Analysenliste and TARMED positions were valued using the simple average of the Swiss cantonal tax point values for 2022.[160]

Resource utilisation data pertaining to OMT and patient follow-up were informed by peer-reviewed literature sources, including ESC guidelines on CCS,[1] a European cohort from an observational registry of CCS patients[155] and the included RCTs.

8.3.1.1 Intervention costs

8.3.1.1.1 PCI

PCIs are performed in both inpatient and outpatient settings. Medical advances are making it increasingly possible for doctors to operate on an outpatient basis; however, Swiss tariff structures may not provide a strong financial incentive for such a shift.[161] Nonetheless, PTCA was listed as 1 of 13 interventions with high outpatient potential in a 2016 report published by PricewaterhouseCoopers (PwC) aimed at valuing the unused potential of outpatient services in Switzerland.[161]

The proportion of patients in Switzerland treated in the outpatient (vs inpatient) setting was set at 22.4%, based on the relative number of inpatient claims for PCI relating to CCS and TARMED claims for position 17.1110 for 2020 (see ***Section 8.3.5.2*** for further details on these data). This proportion was varied in sensitivity analysis using a range of 20–30% for DSA and a beta distribution for PSA, with standard error assumed to equal one-tenth of the mean. Unit costs for inpatient and outpatient PCI procedures were informed by Swiss DRGs and TARMED (***Table 13*** and ***Table 14***, respectively).

8.3.1.1.1.1 Inpatient PCI

The cost for an inpatient PCI procedure was estimated as a weighted average cost for Swiss DRG items F24A to F24F, with weightings based on the number of episodes per year per Swiss DRG version 11.0 calculation data (***Table 13***).[162] For DSA, the lowest and highest mean DRG item costs informed the upper and lower bounds. For PSA, a gamma distribution was assigned, assuming the standard error was equal to one-quarter of the mean cost.

Table 13 Cost per inpatient PCI episode

DRG v11 item	Mean cost (CHF)	Number of episodes
F24A	30,712.80	260
F24B	24,042.65	769
F24C	14,087.10	3,655
F24D	11,441.70	4,051
F24E	11,771.35	3,492
F24F	8,061.00	3,860
Average cost per inpatient PCI (weighted)	**12,216.93**	**16,087**

Abbreviations:
CHF: Swiss franc; **DRG**: diagnosis-related group; **PCI**: percutaneous coronary intervention.

8.3.1.1.1.2 Outpatient PCI

Outpatient PCI procedures were costed according to the combination of TARMED positions shown in ***Table 14***. Mean value was assumed to reflect costs for a patient receiving an average of 1.5 stents across one vascular segment. For DSA, the lower bound assumed no stents were inserted (CHF2,297.09), while the upper bound assumed 3 stents were inserted across 3 vascular segments (CHF3,938.98). For PSA, a gamma distribution was assigned, assuming the standard error was equal to one-quarter of the assumed base case cost.

Table 14 Outpatient PCI unit cost

TARMED position	Description	Tax points (AL + TL)	Number per patient	Cost (CHF)
17.0710	Angiography, basic performance	163.47	1	145.49
17.0740	Cardiography, arterial access, basic performance II	478.00	1	425.42
17.1090	Selective coronary, basic element	447.91	1	398.64
17.1810	Basic technical service 0, cardiac angiography/cardiological-interventional radiology, outpatient	241.97	1	215.35
17.1110	PTCA for coronary stenosis or coronary occlusions, first dilated vascular segment	746.52	1	664.40
17.1130	+ Surcharge PTCA for coronary stenoses or coronary occlusions, any further dilated vascular segment	419.28	0 [A]	0
17.1140	+ surcharge for stent insertion at PTCA, per stent	503.13	1.5 [B]	671.68
Cost per outpatient PCI				2,520.98

Abbreviations:
AL: arztleistung (medical services), **CHF**: Swiss franc; **PCI**: percutaneous coronary intervention; **PTCA**: percutaneous transluminal coronary angioplasty; **TL**: technische leistung (technical performance)
Notes:
One tax point was assumed to have a value of CHF0.89, equal to the simple average of the Swiss cantonal tax point values for 2022.[160]
A = for the upper bound this was increased to 2
B = for the lower bound this was reduced to 1 and increased to 3 for the upper bound

8.3.1.1.2 CABG

CABG procedures are performed in an inpatient setting. Cost per procedure was estimated as a weighted average cost for Swiss DRG items F06A to F06D, with weightings based on the number of episodes per year according to the calculation data of Swiss DRG version 11.0 (***Table 15***).[162] For DSA, the lowest and highest mean DRG item costs informed the upper and lower bounds. For PSA, a gamma distribution was assigned, assuming the standard error was equal to one-quarter of the mean.

Table 15 Cost per CABG episode

DRG v11 item	Mean cost (CHF)	Number of episodes
F06A	51,886.60	101
F06B	48,409.05	373
F06C	39,967.25	268
F06D	35,301.20	773
Average cost per CABG (weighted)	**40,459.52**	**1,515**

Abbreviations:
CABG: coronary artery bypass graft; **CHF**: Swiss franc; **DRG**: diagnosis-related group.

8.3.1.1.3 Revascularisation

For the revascularisation plus OMT vs OMT comparison, cost for the initial invasive procedure was estimated as a weighted average cost for PCI and CABG procedures (***Table 13***, ***Table 14*** and ***Table 15***). Weightings were based on the relative numbers of initial PCI and CABG procedures performed among patients assigned to an initially invasive strategy in the ISCHEMIA trial. Among 2,054 patients who underwent revascularisation, 1,524 (74.2%) underwent PCI while 530 (25.8%) received CABG.[12]

8.3.1.1.4 OMT

ESC guidelines recommend a variety of drug class combinations for CCS patients to manage their symptoms, slow disease progression and/or prevent acute events. These include aspirin, beta-blockers, ACE inhibitors, statins, CCBs, P2Y12 inhibitors and nitrates.[1]

Theoretically, OMT regimens can differ between patients receiving OMT after revascularisation vs those on OMT alone. Discussions with a clinical expert suggest that patients on OMT alone receive a single antiplatelet therapy but a higher antianginal medication load, while patients on OMT after revascularisation require less antianginal medication but will be prescribed DAPT. Complete cessation of antianginal therapy is rare, apart from a period immediately after CABG. However, a cost analysis identified in our systematic literature review found that, in practice, PCI did not affect the cost or use of drugs for angina relief.[135]

Other than changes in antiplatelet and antianginal medications, OMT regimens are similar between groups.[1] Discussions with a clinical expert suggest patients will most likely be prescribed statins and aspirin for life. ACE inhibitors are recommended for patients with certain comorbidities (e.g. HF, hypertension, diabetes). Beta-blockers are recommended for patients with LV dysfunction or systolic HF.[1]

8.3.1.1.4.1 Baseline OMT use

For the present analysis, utilisation of the DAPT drugs aspirin and clopidogrel were considered, along with drugs used for angina therapy (i.e. beta-blockers, CCBs and other antianginal medications). This allowed for potential differences in use before and after revascularisation to be built into the analyses. Use of the remaining components of OMT (statins, other lipid-lowering drugs, ACE inhibitors etc.) was assumed to be similar among patients in the revascularisation plus OMT and OMT-alone arms. As such, these remaining components were omitted from the economic analyses.

Daily costs at the drug class level have been derived using the audience award for drugs listed on the Spezialitätenliste, with dosages assumed to correspond to the WHO's defined daily doses (***Table 16***).[163,164]

Table 16 Unit costs for drug classes included in the economic evaluation

Drug class or preparation	Cost per pack (CHF)	Tablets per pack	Dose per tablet (mg)	Cost per tablet (CHF)	Defined daily dose	Daily cost (CHF)	Yearly cost (CHF)
Aspirin							
Aspirin	14.90	90	100 mg	0.17	1 tablet	0.17	60.40
P2Y12 inhibitor [A]							
Clopidogrel	86.60	84	75 mg	1.03	75 mg	1.03	375.95
Beta-blockers [B]							
Metoprolol	25.95	100	50 mg	0.26	150 mg	0.79	284.15
CCBs [C]							
Amlodipine	41.30	100	5 mg	0.41	5 mg	0.41	150.75
Verapamil	37.95	100	120 mg	0.38	240 mg	0.76	277.04
Diltiazem	39.95	100	120 mg	0.40	240 mg	0.80	291.64
Nitrates and other antianginal drugs [D]							
Nitroglycerin	16.25	200 sprays	0.4 mg per spray	0.08 per spray	2.5 mg, sublingual	0.51	185.35
Isosorbide dinitrate	29.00	100	60 mg	0.29	60 mg, oral	0.29	105.85
Ivabradine	101.55	112	5 mg	0.91	10 mg	1.81	661.89
Nicorandil	26.85	60	20 mg	0.45	40 mg	0.90	326.68
Ranolazine	113.55	100	750 mg	1.14	1,500 mg	2.27	828.92

Abbreviations:
CCB: calcium channel blocker; **CHF**: Swiss franc
Notes:
A = Clopidogrel was considered as the P2Y12 inhibitor that would be prescribed for dual anti-platelet therapy because ESC guidelines recommend clopidogrel 75 mg daily in addition to aspirin, for 6 months following stenting.[1]
B = Metoprolol was considered as the example drug for costing the beta blocker drug class based on it being the only beta blocker among the 15 most expensive or most purchased generics in a 2020 Helsana Drug Report.[165]
C = Amlodipine was considered as an example for the CCB drug class as it was the only CCB among the 15 most expensive or most purchased generics in a 2020 Helsana Drug Report.[165] Verapamil and diltiazem were also considered. Relative use was assumed to be 83.5% amlodipine, 8.25% verapamil and 8.25% diltiazem, based on baseline drug utilisation among the Austrian cohort of the CLARIFY registry.[166]
D = The nitrates considered were included in both ESC guidelines and are authorised in Switzerland.[1,167] For other antianginal drugs, ivabradine, nicorandil and ranolazine were included in the CLARIFY registry, ESC guidelines and are authorised in Switzerland.[1,155,167] An

equal distribution across the 5 drugs was assumed for costing purposes. It should be noted that these represent different lines of antianginal medication.[168]

Proportions of the hypothetical model cohort using each drug at baseline were informed by baseline utilisation data among western/central European patients from the CLARIFY registry (***Table 17***).[155]

Table 17 Assumed baseline utilisation of OMT, drug class level

Drug class	OMT alone (% cohort)
Single antiplatelet therapy [A]	95.1
DAPT	25.3
Beta-blockers	77.0
CCB	26.2
Other antianginal medications	25.2

Abbreviations:
CCB: calcium channel blocker; **DAPT**: dual anti-platelet therapy; **OMT**: optimal medical therapy
Notes:
A = Not all single antiplatelet therapy use within the cohort was attributable to aspirin (85.6% were taking aspirin); however, the assumption was made to cost single antiplatelet therapy as aspirin use and DAPT as aspirin plus clopidogrel.
Source:
Proportion of the cohort utilising each drug class was sourced from baseline utilisation data among western/central European patients included in the CLARIFY registry.[155]

8.3.1.1.4.2 Changes in OMT use after revascularisation

In the period immediately following revascularisation, it was assumed that all patients would receive DAPT for 6 to 12 months (average of 9 months used in calculations) following PCI. In addition, it was assumed that all patients requiring subsequent revascularisation with PCI or suffering an MI would receive DAPT for 6 to 12 months (average of 9 months used in calculations) in line with ESC guidelines.[1]

It was assumed that only 50% (range: 0–100%) of patients initially using 'other' antianginal medications would require them in the 5 years after revascularisation (10 years for CABG). Use of beta-blockers and CCBs was assumed to remain the same before and after revascularisation.

These assumptions are summarised in ***Table 18***.

Table 18 Input parameters for assumed changes in OMT use after revascularisation

Parameter	Mean	Range	Distribution	Description
Use of antianginal drugs after revascularisation	0.50	0 to 1.00	Beta SE: 0.2551	Arbitrary assumption 50% (0-100%) patients initially using antianginal medications would require them in the 5 years (10 years for CABG) after revascularisation
Proportion of patients receiving DAPT after a PCI procedure or MI	1.00	0.50 to 1.00	NA	Assumption that 100% (50-100%) patients would require DAPT after PCI or MI.

Abbreviations:
DAPT: dual anti-platelet therapy; **NA**: not applicable; **MI**: myocardial infarction; **PCI**: percutaneous coronary intervention; **SE**: standard error.

8.3.1.2 Patient follow-up costs

Resource utilisation associated with patient follow-up after revascularisation was informed by ESC guidelines.[1] Unit costs for physician visits, laboratory analyses and other tests (i.e. electrocardiogram and echocardiograms—resting or stress) conducted in the outpatient setting were informed by TARMED and the Analysenliste (***Table 19***).

According to ESC guidelines, patients should undergo at least 2 follow-up visits in the year after CCS diagnosis, revascularisation or stabilised ACS (<1 year) to monitor for complications and reassess pharmacological treatments (e.g. DAPT continuation in PCI patients).[1] Soon after revascularisation (1–3 months), echocardiography at rest or stress testing for inducible ischaemia may be considered to assess changes after revascularisation or to set a reference value for future assessments.[1] In the current evaluation, follow-up costs in the first year after revascularisation or MI were assumed to include 2 GP visits with resting ECGs and an echocardiogram (at rest [in 50% of patients] or under stress [in 50% of patients]) in half of the cohort (***Table 19***).

For patients with a long-standing (>1 year) CCS diagnosis, including patients at >1 year after revascularisation or MI, at least one evaluation annually is recommended to assess overall clinical status, medication compliance and risk profile.[1] Laboratory tests, including lipid profile, renal function, complete blood count and possibly biomarkers, are recommended every 2 years, while a 12-lead ECG should be part of every visit.[1] Echocardiography at ischaemic rest to evaluate LV function, valvular status and haemodynamic status, and stress testing (preferably using stress imaging) to reassess ischaemia may be performed periodically (every 3-5 years).[1] In this analysis, follow-up costs for patients at >1 year after revascularisation or MI and for patients receiving OMT alone, included costs for an annual GP visit and ECG, bi-annual blood test, and echocardiography every 4 years (***Table 19***).

Table 19 Patient follow-up cost inputs

Item	Mean cost (CHF)	Comments
Unit costs		
Unit cost for GP visit (20-min consult + 5-min review of files)	84.20	TARMED positions 00.0010, 0.0015, 0.0020, 00.0030, and 00.0141
Unit cost for resting ECG	30.20	TARMED position 17.0010
Unit cost for echocardiography (without contrast)	390.10	TARMED position 17.0210
Stress echocardiography	325.40	TARMED position 17.0280
Blood tests (not including markers)	79.48	TARMED position 00.0715 and Analysenliste positions 12300.00, 1230.01, 1410.01, 1410.10, 1731.00, 1731.01, 1521.00, 1509.00, 1509.01, 1363.00, and 1363.01
Annual follow-up costs		
After REV or MI	407.68	2 GP visits, 2 ECGs + echocardiography (at rest or under stress) in 50% of the cohort

Item	Mean cost (CHF)	Comments
Standard CCS follow-up	243.58	1 GP visit, 1 ECG, biannual blood tests + echocardiography (at rest or under stress) every 4 years.

Abbreviations:
CHF: Swiss franc; **ECG:** electrocardiogram; **MI**: myocardial infarction; **REV**: revascularisation.

8.3.1.3 Clinical event costs

The occurrence of clinical events (i.e. revascularisation, MI, stroke, hospitalisation for HF) within a hypothetical cohort was modelled using data from the clinical review and economic modelling. Unit costs, informed by Swiss DRGs and TARMED, were assigned to each clinical event (***Table 20***).

Table 20 Clinical event cost inputs

Event	Unit cost (CHF)	Source
MI	8,786.64	DRG items F41A-B and F60A-B
REV	15,577.80 (after REV) 20,520.25 (after OMT)	DRG items F06A-D and F24A-F, and TARMED positions 17.0710, 17.0740, 17.1090, 17.1810, 17.1110, 17.1130 and 17.1140.
Hospitalisation for HF	10,907.10	F62A-D
Stroke	12,432.44	B39A-C, B70A-G and B70J-K

Abbreviations:
CHF: Swiss franc; **DRG**: diagnosis-related group; **HF**: heart failure; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **REV**: revascularisation.

8.3.1.3.1 Myocardial infarction

Cost per MI episode was estimated as a weighted average cost for Swiss DRG items F41A–B and F60A–B, with weightings based on the number of episodes per year per Swiss DRG version 11.0 calculation data (***Table 21***).[162] For DSA, the lowest and highest mean individual DRG item costs informed the upper and lower bounds. For PSA, a gamma distribution was assigned, assuming the standard error was equal to one-quarter of the weighted average cost.

Table 21 Cost per inpatient MI episode

DRG v11 item	Mean cost (CHF)	Number of episodes
F41A	17,728.15	255
F41B	8,576.15	963
F60A	12,423.00	428
F60B	6,927.00	1,954
Average cost per MI (weighted)	**8,786.64**	3,600

Abbreviations:
CHF: Swiss franc; **DRG**: diagnosis-related group; **MI**: myocardial infarction.

8.3.1.3.2 Revascularisation

The cost per subsequent revascularisation episode was estimated as a weighted average cost for PCI and CABG procedures (***Table 13***, ***Table 14*** and ***Table 15***). Weightings were based on numbers of PCI and CABG procedures reported in the ISCHEMIA trial performed in the invasive therapy group.[12] This weighting (0.74 PCI in the base case) was included as a beta distribution for PSA, with the standard error assumed to equal one-tenth of the mean estimate.

8.3.1.3.3 Hospitalisation for HF

The cost per HF episode was estimated as a weighted average cost for Swiss DRG items F62A–D, with weightings based on the number of episodes per year per the calculation data of Swiss DRG version 11.0 (***Table 22***).[162] For DSA, the lowest and highest mean individual DRG item costs informed the upper and lower bounds. For PSA, a gamma distribution was assigned, assuming the standard error was equal to one-quarter of the weighted average cost.

Table 22 Cost per hospitalisation for HF episode

DRG v11 item	Mean cost (CHF)	Number of episodes
F62A	25,297.25	102
F62B	19,826.55	280
F62C	15,307.95	2,828
F62D	9,321.05	10,347
Average cost per HF hospitalisation	**10,907.10**	13,557

Abbreviations:
CHF: Swiss franc; **DRG**: diagnosis-related group; **HF**: heart failure.

8.3.1.3.4 Stroke

The cost per revascularisation episode was estimated as a weighted average cost for Swiss DRG items B39A–C, B70A–G, B70J and B70K, with weightings based on the number of episodes per year per Swiss DRG version 11.0 calculation data (***Table 23***).[162] For DSA, the lowest and highest mean individual item costs informed the upper and lower bounds. For PSA, a gamma distribution was assigned, assuming the standard error was one-quarter of the weighted average cost.

Table 23 Cost per inpatient stroke episode

DRG v11 item	Mean cost (CHF)	Number of episodes
B39A	46,224.25	112
B39B	33,610.85	285
B39C	27,431.30	552
B70A	25,279.70	302
B70B	17,931.10	360
B70C	14,794.15	894
B70D	13,841.75	1,781
B70E	12,128.95	677
B70F	12,693.90	904
B70G	9,927.00	3,431
B70J	6,414.90	104
B70K	3,363.44	2,138
Cost per stroke patient	**12,432.44**	11,540

Abbreviations:
CHF: Swiss franc; **DRG**: diagnosis-related group.

8.3.2 Clinical evidence

Defining a 'typical' CCS patient for the model proved challenging. As discussed below (***Section 8.3.2.1***), there is uncertainty in the alignment of the general CCS population with our target population (i.e. CCS patients being considered for revascularisation) and in defining PCI- and CABG-specific cohorts.

Discussions with a clinical expert emphasised the heterogeneity among CCS patients in practice. In general, the RCTs included in this HTA reflect diverse patient subgroups. Given differences in eligibility criteria across the included RCTs, individual studies were considered separately when defining the baseline risk of MACE for the control arm of the model (i.e. patients receiving OMT alone) (***Section 8.3.2.2***). To capture differing baseline risks of MACE, subgroup analyses sourcing baseline risks from the OMT-alone arms of several individual trials were undertaken.

Estimates of treatment effect were drawn from the clinical review and associated meta-analyses (***Section 8.3.2.3***), it being assumed that an overall estimate of relative effect could be applied to trial-specific baseline event rates.

8.3.2.1 Applicability of the evidence

8.3.2.1.1 Patients with CCS

Data from the CLARIFY registry, which enrolled 32,703 outpatients with CCS across 45 countries in 6 geographical areas (including 286 Swiss patients), provides some insight into the general characteristics of CCS patients.[155,169] Included patients had either a history of MI, PCI or CABG >3 months earlier, at least one coronary stenosis of >50%, and/or chest pain with proven myocardial ischaemia.[155,169] Among

the western/central European cohort (n = 15,301), 58.1% had a history of MI, while 64.5% and 26.1% had a history of PCI or CABG, respectively.[155] Angina symptoms were present in 16.7% of the western/central European cohort.[155]

Defining the revascularisation-suitable CCS cohort is challenging. One uncertainty lies in understanding exactly how CCS patients are identified in Switzerland—those presenting after an ACS event or those without ACS presenting with signs and/or symptoms of the disease (i.e. ischaemia, angina and atherosclerotic plaque accumulation in coronary arteries). Among some RCT cohorts included in the clinical review, there were lower rates of MI or prior revascularisation (***Table 24***). Moreover, the decision to pursue an invasive approach (i.e. revascularisation) is patient specific. Indications according to the presence or absence of symptoms and the presence of documented ischaemia can be summarised; however, the individual risk-benefit ratio should always be considered.[1]

Table 24 Prior MI and revascularisation among included RCT cohorts

	History of MI (%)	Prior PCI (%)	Prior CABG (%)	Comments
CLARIFY registry				
western/central European cohort	58.1	64.5	26.1	Prospective observational study of patients with CCS
Revascularisation + OMT vs OMT				
ISCHEMIA	19.2	20.3	3.9	RCT of patients with moderate to severe myocardial ischaemia
ISCHEMIA–CKD	17.1	18.8	3.6	RCT of patients with moderate to severe myocardial ischaemia and advanced kidney disease
BARI-2D	32.0	23.6 with prior REV		RCT of patients with CCS and diabetes
PCI + OMT vs OMT				
BARI-2D	30.1	28.6 with prior REV		RCT of patients with CCS and diabetes (Randomisation stratified by planned REV approach)
EUROCTO	21.2	Prior PCI unrelated to study: 54.5 [A]	11.1	RCT of symptomatic patients with ≥1 CTO suitable for PCI
FAME 2	37.5	PCI in target vessel: 17.6	NR	RCT of patients with 1-, 2- or 3-vessel CCS suitable for PCI with ≥1 stenosis with FFR ≤0.80
Hennigan et al.	50	61.5	NR	RCT of patients with clinical indication for pressure wire-based evaluation of intermediate coronary lesion (30–80% diameter stenosis by visual assessment) and with FFR value 0.75–0.82
CABG + OMT vs OMT				
BARI 2D	36.0	13.0 with prior REV		RCT of patients with CCS and diabetes (Randomisation stratified by planned REV approach)

	History of MI (%)	Prior PCI (%)	Prior CABG (%)	Comments
STICH	77.1	NR	3.0	RCT of patients with CCS amenable to CABG and LVEF ≤35%

Abbreviations:
BARI-2D: Bypass Angioplasty Revascularisation Investigation 2 Diabetes; **CABG**: coronary artery bypass surgery; **CCS**: chronic coronary syndrome; **CKD**: chronic kidney disease; **CLARIFY**: Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease; **CTO**: coronary total occlusion; **FAME-2**: Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2; **FFR**: fractional flow reserve; **ISCHEMIA**: International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; **LVEF**: left ventricular ejection fraction; **MI**: myocardial infarction; **NR**: not reported; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **RCT**: randomised controlled trial; **REV**: revascularisation; **STICH**: Surgical Treatment for Ischemic Heart Failure.
Notes:
A: In addition, 29.3% of cohort had PCI to facilitate study entry. Eligible patients with multivessel disease first receive treatment of any significant non-CTO lesions >4 weeks before baseline assessment and randomisation.[117]

8.3.2.1.2 Choice of PCI vs CABG in patients with CCS

Understanding how patients are selected for PCI or CABG in Switzerland is uncertain. This leads to uncertainty in understanding the demographic and clinical characteristics that individually define the PCI and CABG cohorts.

ESC guidelines state that predicted surgical mortality, anatomical complexity of CAD and anticipated completeness of revascularisation are important criteria for decision-making.[37] Individual cardiac and extracardiac characteristics along with patient preferences should also be taken into account.[37] One- or 2-vessel disease without proximal LAD coronary artery stenosis may favour PCI, while either procedure is indicated when proximal LAD stenosis exists.[37] In the setting of multivessel disease and/or left main coronary artery disease, clinical characteristics such as diabetes and reduced LVEF (≤35%) may favour CABG, as does a SYNTAX score of ≥23 (PCI may be appropriate if SYNTAX score is 0–22 in the absence of diabetes).[37] In patients with HF and LVEF ≤35%, CABG is preferred (PCI can be considered as an alternative).[37]

PCI- and CABG-specific RCTs included in the clinical review are listed above (***Table 24***).

8.3.2.2 Sources of evidence for baseline event rates

8.3.2.2.1 Base-case estimates

Baseline event rates were derived from 5-year cumulative event probabilities reported in the OMT arm of the ISCHEMIA trial.[12] The ISCHEMIA trial randomised 5,179 patients with CCS and moderate or severe ischaemia to an invasive strategy of OMT, angiography and revascularisation (PCI or CABG) when feasible, or to a conservative strategy of OMT alone.[12,168]

Event rates observed in the OMT-alone arm (n = 2,591) were considered to reflect event rates among a general patient cohort otherwise suitable for revascularisation (PCI or CABG). Other RCTs were specific to certain subpopulations (i.e. patients with chronic kidney disease or diabetes; ***Table 24***).[104,170]

Five-year cumulative event probabilities for the OMT arm of the ISCHEMIA trial are shown in ***Table 25***. These were converted to annual transition probabilities using the following steps:[171]

- conversion to annual rates using the formula $r = -1/5\ LN(1-p)$
- conversion of the annual rates to annual probabilities using the formula $p = 1 - EXP(-r \times 1)$.

Table 25 5-year cumulative event probabilities from the ISCHEMIA RCT

Event	OMT alone
Death from any cause	8.3%
Any MI	11.9%
Any stroke	2.4%
Revascularisation [A]	18.3%
Hospitalisation for HF	1.6%

Abbreviations:
HF: heart failure; **MI**: myocardial infarction; **OMT**: optimal medical therapy.
Notes:
A: Reflects rates of revascularisations not preceded by confirmed MI, unstable angina, HF or resuscitated cardiac arrest.

Fatal MIs and strokes were subtracted from the derived MI and stroke transitions, as any fatal events would be reflected in the all-cause mortality estimates. In the ISCHEMIA trial, the 30-day case fatality rate for MI was 7.2%.[172] Stroke fatality rates were not reported. In Switzerland in 2004, the overall case fatality rate for patients hospitalised for stroke (ICD 10 codes I60 to I64) was 22.7% (95% CI: 21.9 to 23.4).[173] This rate was assumed to reflect the stroke fatality rate within the model cohort.

8.3.2.2.2 Alternative estimates for subgroup analysis

There are concerns that the ISCHEMIA trial cohort represents a highly selected CCS population that presents a low annual risk of MACE.[174,175] The ISCHEMIA trial excluded patients with advanced kidney disease, unprotected left main stenosis ≥50%, LVEF ≤35%, HF (New York Heart Association class III or IV) or unacceptable angina despite the use of medical therapy at maximum acceptable doses.[12] A recent study assessing the applicability of the ISCHEMIA trial to an Italian registry of over 5,000 CCS patients found that only 3.8% of registry patients fulfilled the ISCHEMIA trial inclusion criteria, had no exclusion criteria, and presented at least 50% stenosis in ≥1 major coronary artery within 6 months of enrolment.[174] However, it has been questioned whether the Italian registry cohort is representative of real-world CCS patients given a large percentage (i.e. 67.5%) had only been included because of an ACS ≥30 days before enrolment and many (i.e. 73.2%) had no angina at baseline.[175] A retrospective analysis of 1,000 consecutive PCIs performed at a Swiss university hospital found that, among patients with CCS undergoing PCI (n = 320), 71.6% would have been excluded from the ISCHEMIA trial due to the presence of at least one exclusion criterion—most commonly, a history of ACS within the last 2 months or a prior PCI or CABG procedure in the previous 12 months.[176]

Separate trials have considered populations limited to patients with CCS and advanced kidney disease or CCS and LVEF ≤35%.[104,115] Baseline event rates from these studies were considered in subgroup analyses—the latter (i.e. patients with LVEF ≤35%) for a CABG-specific analysis. For PCI, a subgroup analysis considering patients with high event risk, based on invasive functional testing (i.e. FFR ≤0.8),[1] was also considered.

8.3.2.2.2.1 Patients with chronic kidney disease

The ISCHEMIA–CKD trial randomly assigned 777 patients with advanced kidney disease—defined as either an estimated glomerular filtration rate <30 ml/min/1.73 m^2 of body surface area or dialysis-dependent—and moderate or severe ischaemia to an initial invasive strategy (coronary angiography and revascularisation if appropriate) plus OMT or an initial conservative strategy of OMT alone.[104] These patients were excluded from the main ISCHEMIA trial, so a subgroup analysis using baseline event rates derived from the ISCHEMIA–CKD trial was undertaken. Three-year cumulative event probabilities for the OMT arm are shown in ***Table 26***. These were converted into annual transition probabilities, accounting for fatal MI and stroke (see ***Section 8.3.2.2.1***).

Table 26 3-year cumulative event probabilities from the ISCHEMIA–CKD RCT

Event	OMT alone
Death from any cause	27.8%
Any MI	15.9%
Any stroke	1.6%
Revascularisation [A]	11.1%
Hospitalisation for HF	3.6%

Abbreviations:
HF: heart failure; **MI**: myocardial infarction; **NR:** not reported **OMT**: optimal medical therapy.
Notes:
A: Reflects rates of revascularisations not preceded by confirmed MI, unstable angina, HF or resuscitated cardiac arrest.

8.3.2.2.2.2 Patients with reduced left ventricular function (CABG only)

The STICH trial enrolled patients with CCS with LVEF ≤35%.[115] According to ESC guidelines, CABG is preferred (PCI can be considered an alternative) in patients with HF and LVEF ≤35% (***Section 8.3.2.1.2***).[1] CCS patients with LVEF ≤35% were excluded from the ISCHEMIA trial,[12] therefore a subgroup analysis using baseline event rates derived from the STICH trial was undertaken.

Ten-year cumulative event probabilities for the OMT are shown in ***Table 27***. These were converted into annual transition probabilities, accounting for fatal MI and stroke (see ***Section 8.3.2.2.1***).

Table 27 10-year event probabilities from the STICH RCT

Event	OMT alone
Death from any cause	66.1%
Any MI	9.1%
Any stroke	6.8%
Revascularisation	16.6% [A]
Hospitalisation for HF	13.3%

Abbreviations:
HF: heart failure; **MI**: myocardial infarction; **OMT**: optimal medical therapy
Notes:
A: Rate of revascularisation reflects the rate at 5 years (not 10 years).

8.3.2.2.2.3 Patients with high event risk based on FFR (PCI only)

Baseline transitions from the ISCHEMIA trial were considered to reflect event rates among a general patient cohort considered otherwise suitable for revascularisation (PCI or CABG). In practice, however, different patient cohorts are selected for PCI vs CABG depending on individual cardiac and extracardiac characteristics and patient preference (***Section 8.3.2.1.2***).[1]

The FAME 2 trial randomly assigned 888 PCI-suitable patients with 1-, 2- or 3-vessel CAD and at least one stenosis with FFR ≤0.80 to receive PCI plus OMT (DES for all stenoses with FFR ≤0.80) or OMT alone.[108] FFR ≤0.80 on invasive functional testing is noted in ESC guidelines as signalling a high risk of an event.[1] Without documented ischaemia and with or without angina symptoms, FFR ≤0.80 is considered an indication for revascularisation.[1] For all patients in the FAME 2 trial, PCI was the preferred strategy (patients for whom CABG was the preferred strategy were excluded).[108]

Data from the FAME 2 trial were considered in a subgroup analysis for PCI among patients with a high event risk based on invasive functional testing (i.e. FFR ≤0.8).[1] Five-year event probabilities for the OMT arm are shown in ***Table 28***. These were converted to annual transition probabilities, accounting for fatal MIs and strokes (see ***Section 8.3.2.2.1***).

Table 28 5-year event probabilities from the FAME 2 RCT

Event	OMT alone
Death from any cause	5.2%
Any MI	12.0%
Any stroke	1.6%
Revascularisation [A]	35.1%
Hospitalisation for HF	NR [B]

Abbreviations:
HF: heart failure; **MI**: myocardial infarction; **NR:** not reported **OMT**: optimal medical therapy.
Notes:
A: Reflects rate of non-urgent revascularisations only
B: Due to an absence of data, this was assumed equivalent to the 5-year cumulative probability from the ISCHEMIA RCT which informed the baseline transition probability in the base case.[12]

8.3.2.2.3 Assumptions regarding baseline event rates

Regarding the baseline transition probabilities (i.e. transition probabilities for patients receiving OMT alone), all transitions apart from mortality (all causes) were assumed to be constant over time. Transitions from any of the alive states to dead were linked to age. Risks of all other MACE events were assumed to remain constant, regardless of patient age or duration of CCS.

Baseline mortality transitions were assumed to reflect all-cause mortality in a CCS population with the same age and gender breakdown as the source RCT. The start age of the model cohort was set equal to the mean or median age of the source RCT population (e.g. 64 years for the ISCHEMIA trial). Mortality transitions were adjusted in 5-yearly intervals as the model cohort aged.

The background mortality rate for the general Swiss population of the same age as the assumed start age of the model cohort was subtracted from the annual all-cause mortality rate to derive disease-specific mortality. Age-based adjustments to the baseline mortality transition were made by increasing the background mortality portion of the all-cause mortality rate in line with mortality rate increases in the general Swiss population.

8.3.2.3 Sources of evidence for treatment effects

Treatment effectiveness was incorporated by applying risk ratio estimates reported or derived as part of the clinical review for revascularisation plus OMT vs OMT, PCI plus OMT vs OMT and CABG plus OMT vs OMT (***Section 7.4***). For each outcome, the risk ratio reported at the timepoint of longest follow-up was used.

8.3.2.3.1 Assumptions regarding the application of treatment effect estimates

Transition probabilities for the revascularisation arm were derived over 2 distinct time periods: the first reflected the period over which the effects of revascularisation were present; the second reflected the period beyond this (i.e. beyond the timepoint at which the effects of revascularisation were assumed to wane).

Over the period for which evidence on the relative treatment effects of invasive intervention vs OMT alone was available (5 years for revascularisation and PCI; 10 years for CABG), transition probabilities were derived by multiplying baseline annual event rates by estimated risk ratios. The estimates of relative treatment effect derived at 60 months for revascularisation and PCI and at 120 months for CABG were selected and applied. An assumption was made that a constant transition probability could be applied across the entire 5- or 10-year period.

Beyond the periods of trial follow-up, transitions probabilities were assumed to be equivalent across the invasive intervention(s) and OMT-alone arms. Estimates of relative treatment effect were no longer

applied; it being assumed that any observed treatment effects would cease after trial follow-up. Thus, beyond trial follow-up, transition probabilities across the OMT alone and revascularisation plus OMT arms were equivalent.

8.3.3 Health state utilities

8.3.3.1 Utility for CCS patients

QoL data were reported by 4 of the included RCTs: EUROCTO,[117] Hennigan et al.,[110] ISCHEMIA,[12,112] and STICH.[111]

The EUROCTO trial assessed cardiac-specific health status using the SAQ and general health status using the EQ-5D visual analogue scale (VAS) with domain-specific response percentages within the cohort that could not be translated into utilities.[117] Hennigan et al. assessed cardiac-specific health status using the SAQ (reported as baseline SAQ scores and change from baseline).[110] In the ISCHEMIA trial, the entire cohort completed the SAQ-7 (shortened form that captures angina frequency, physical limitations and disease perception/QoL domains), while a comprehensive QoL sub-study was limited to patients randomised from the US, Canada and 11 other countries.[12,112,177] In the QoL sub-study, the following survey instruments were used: SAQ (angina stability domain not reported), EQ-5D VAS, Rose Dyspnoea Scale and Patient Health Questionnaire-8 (PHQ-8).[112] In the STICH trial, the following instruments were used: Kansas City Cardiomyopathy Questionnaire (KCCQ), 3 scales from the SAQ, SF-12 and -5 individual scales from the SF-36, Centre for Epidemiologic Studies Depression Scale, Cardiac Self-Efficacy Questionnaire, EQ-5D (VAS and health status index both reported on scale 0–100).[111]

A prediction algorithm that maps the 5 SAQ component scores to an EQ-5D utility has previously been published and subsequently used to create a catalogue of estimated health utility scores from the ischaemic heart disease literature.[178,179] This algorithm was used to map SAQ component scores to EQ-5D utilities.

We focused on mapping SAQ to EQ-5D utilities over other general or cardiac-specific measures (e.g. SF-12 or KCCQ), given this scale was used across all RCTs reporting HRQoL outcomes. SAQ is a common measure of coronary artery disease-specific health status that can be used to quantify angina symptoms and the degree to which angina impacts function and HRQoL.[180] Details on the algorithm itself are provided in ***Appendix F*** (***Section 19.4***).

To inform baseline utility for patients with CCS, SAQ component scores reported among a cohort of Austrian patients with stable angina (n = 660) were mapped to EQ-5D utility using the prediction algorithm (***Section 8.3.3.1.1***).[179,181] The relative effect of revascularisation (vs OMT alone) on component scores was also considered (***Section 8.3.3.1.2***).

8.3.3.1.1 SAQ component scores and mapped utility for a cohort of Austrian CCS patients

Between September and November 2017, 660 Austrian patients with stable angina pectoris were enrolled in an observational survey from 70 sites (across all 9 Austrian provinces and both urban and rural areas) including GPs, specialists for internal medicine and outpatient clinics.[181] Enrolled patients completed the SAQ as a measure of functional status and life satisfaction. Main inclusion criteria comprised MI >3 months previously, coronary stenosis >50% by coronary arteriography, chest pain with myocardial ischaemia, and/or CABG or PCI >3 months previously.[181] Across the cohort (n = 660), mean age was 69.2 years (SD 10.7 years) and BMI was 27.9 kg/m^2 (SD 4.1 kg/m^2); 70.3% were male, 63.6% had a history of PCI with stent, 22.3% had a history of CABG and 46.1% had a history of MI. The algorithm discussed above was used to map SAQ component scores from this cohort to EQ-5D index scores (***Table 29***).

Table 29 Assumed baseline SAQ component scores and mapped EQ-5D utility

Health-related quality of life instrument	Value
SAQ component scores (mean [SD])	
Physical limitation	67.5 (24.4)
Angina frequency	79.3 (23.2)
Angina stability	65.5 (26.6)
Treatment satisfaction	86.3 (16.2)
Quality of life [A]	63.7 (24.2)
EQ-5D utility (predicted)	
Mapped EQ-5D utility	0.814

Abbreviations:
EQ-5D: European quality of life 5-dimension questionnaire; **SAQ**: Seattle Angina Questionnaire; **SD:** standard deviation.
Notes:
A = This domain referred to interchangeably as either quality of life or disease perception.[180]
Source:
SAQ component scores were sourced from an Austrian cohort.[181] Predicted EQ-5D scores were derived using a published mapping algorithm.[179]

Uncertainty in the baseline utility estimate was indirectly captured in both DSA and PSA, with uncertainty ranges and distributions being assigned to the SAQ component score inputs and the parameters of the mapping algorithm. Both the SAQ component scores and the mapping algorithm parameters were assigned normal distributions for PSA.

Means and SDs of the SAQ component scores were reported.[181] The standard errors used in the assigned normal distributions were derived from the standard deviations and sample size (n = 660). The bounds of the 95% CI from the assigned normal distributions informed the lower and upper values used in DSA.

Means and 95% credible intervals were reported for the parameters of the mapping algorithm.[179] These were used as the upper and lower values in DSA and to derive the standard errors used in the assigned normal distributions.

8.3.3.1.2 Treatment effect on health-related quality of life

To account for the effects (if any) of revascularisation (PCI or CABG) on patient HRQoL, mean difference in each SAQ component reported or estimated as part of the clinical review (summarised in ***Table 30***) was applied to baseline SAQ component scores prior to the scores being mapped into an EQ-5D utility. Any effects of invasive intervention on angina symptoms and HRQoL were assumed to attenuate after follow-up—60 months for revascularisation plus OMT and CABG plus OMT,[111,112] and 12 months for PCI plus OMT.[110,117]

For revascularisation plus OMT, data on the effect of invasive intervention on angina stability were missing (***Table 30***). In the absence of these data, it was conservatively assumed that revascularisation plus OMT would have no effect relative to OMT alone with respect to this domain.

For CABG plus OMT, data on the effect of invasive intervention on angina stability, physical limitations and treatment satisfaction were missing (***Table 30***). Treatment effect estimates from the revascularisation plus OMT arm were used for the physical limitations and treatment satisfaction domains, while it was assumed that CABG plus OMT would have no effect relative to OMT alone with respect to angina stability.

Table 30 Differences in SAQ component score between intervention and comparator during follow-up

Domain and timepoint of analysis (months)	Revascularisation + OMT MD (95% CI)	PCI + OMT MD (95% CI)	CABG + OMT MD (95% CI)
Angina frequency			
12	1.80 (0.41 to 3.19)	3.94 (0.29 to 7.59)	6.60 (4.05 to 9.15)
24	1.45 (-0.11 to 3.01)	NR	4.00 (1.45 to 6.55)
60	0.82 (-1.02 to 2.66)	NR	1.30 (-1.29 to 3.89)
Angina stability			
12	NR	1.04 (-3.10 to 5.17)	NR
Quality of life			
12	3.56 (1.65 to 5.47)	4.98 (0.25 to 9.71)	6.70 (3.76 to 9.64)
24	1.97 (-0.09 to 4.03)	NR	6.80 (3.59 to 10.01)
60	0.47 (-2.17 to 3.11)	NR	2.40 (-0.74 to 5.54)
Physical limitations			
12	1.25 (-0.72 to 3.22)	4.79 (0.35 to 9.22)	NR
24	1.57 (-0.74 to 3.88)	NR	NR
60	0.18 (-3.00 to 3.36)	NR	NR
Treatment satisfaction			
12	1.97 (0.66 to 3.28)	1.22 (-1.64 to 4.07)	NR
24	1.71 (0.30 to 3.12)	NR	NR
60	0.26 (-1.59 to 2.11)	NR	NR

Abbreviations:
CABG: coronary artery bypass graft; **MD**: mean difference; **NR**: not reported; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **SAQ:** Seattle Angina Questionnaire.

Mapped EQ-5D utilities for patients in the years following a revascularisation procedure are summarised in ***Table 31***.

Table 31 Mapped EQ-5D utilities in the 5 years following invasive intervention

Timepoint (months)	Revascularisation + OMT	PCI + OMT	CABG + OMT
0 to 12	0.827	0.839	0.839
12 to 24	0.824	0.814 [A]	0.838
24 to 60	0.817	0.814 [A]	0.822
>60	0.814 [A]	0.814 [A]	0.814 [A]

Abbreviations:
CABG: coronary artery bypass surgery; **CCS**: chronic coronary syndrome; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **SAQ**: Seattle Angina Questionnaire.
Notes:
A = patient utility was assumed to return to the baseline estimate for CCS patients (i.e. 0.814) beyond the last reported data point for difference in SAQ component scores—i.e. beyond 12 months following PCI and beyond 5 years for revascularisation and CABG.

Uncertainty in the post-revascularisation utilities was captured indirectly in both DSA and PSA via the uncertainty ranges and distributions assigned to the baseline SAQ component scores (as described above), mapping algorithm parameters (as described above), and the difference in SAQ component score estimates.

Means and 95% CIs for the difference in SAQ component score inputs were reported (***Table 30***). The parameters of the 95% CIs informed the lower and upper values used in DSA. For PSA, normal distributions were assigned. Standard errors were derived from the reported 95% CIs.

8.3.3.2 Event-related disutility

A pragmatic approach was taken to identify event-related disutility data, starting with a review of known model-based cost-effectiveness studies on the topic.

A research article retrieved from the reference list of one of the included cost-effectiveness analyses estimated utilities of health states associated with cardiovascular conditions (stroke, HF and ACS).[134,182] The study distinguished between the acute impact of the event (i.e. heath state utility in the year following the event) and the chronic post-event impact (defined as health state utility over a 10-year time horizon).[182] Health states were valued by general population participants in the UK, using the time trade-off method.

The acute health utility states valued in this study informed the health state utilities included in our model. In the model, patients remained in a temporary post-event state for one cycle (i.e. 1 year) before returning to the well-with-CCS state or transitioning to death (see ***Section 8.1.4.2***). Health state utility for ACS was assumed applicable for both the MI and revascularisation health states. Standard errors were estimated from the reported standard deviation and population size (n = 200) to inform 95% CI for DSAs and probability distributions for PSAs. Beta distributions were assumed for all utility estimates (***Table 32***).

Table 32 Assumed health state utilities for included clinical events

Cardiovascular event	Acute heath state; mean (SD) utility[182]
ACS	0.67 (0.34)
Stroke	0.33 (0.46)
HF	0.60 (0.38)

Abbreviations:
ACS: acute coronary syndrome; **SD:** standard deviation; **HF**: heart failure.
Notes:
Health state utility scores were valued by 200 participants from the general population using the time trade-off method.

8.3.4 Findings: cost-effectiveness

8.3.4.1 Findings revascularisation plus OMT vs OMT

8.3.4.1.1 ICER

Incremental cost-effectiveness of revascularisation (i.e. PCI or CABG) plus OMT vs OMT alone over 5-year (i.e. longest follow-up) and lifetime time horizons is presented in ***Table 33***. Revascularisation plus OMT was associated with higher expected per patient costs, life years (LYs) and QALYs relative to OMT alone. ICERs of CHF445,228 and CHF202,589 were calculated over the 5-year and lifetime time horizons, respectively (***Table 33***).

Table 33 Incremental cost-effectiveness of revascularisation plus OMT vs OMT

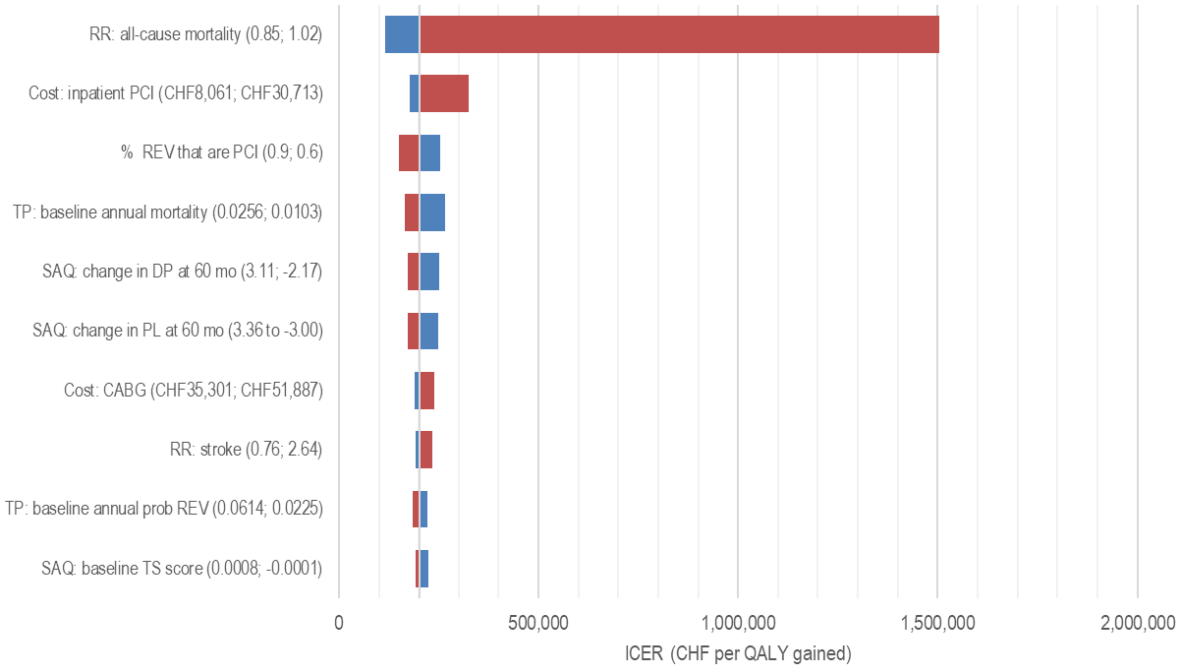
	5-year horizon		Lifetime horizon (36 years)	
	Revascularisation + OMT	OMT alone	Revascularisation + OMT	OMT alone
Expected cost per patient (CHF)	24,352.29	7,693.03	40,402.82	23,637.68
Incremental cost (CHF)	16,659.26		16,765.14	
Expected LYs per patient	4.446	4.433	13.681	13.612
Incremental LYs	0.013		0.069	
Expected QALYs per patient	3.604	3.566	11.019	10.936
Incremental QALYs	0.037		0.083	
ICER (cost per QALY gained)	445,227.90		202,588.83	

Abbreviations:
CHF: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **LY**: life year; **OMT**: optimal medical therapy; **QALY**: quality-adjusted life year; **REV**: revascularisation.

8.3.4.1.2 Univariate sensitivity analysis

Univariate DSAs were used to identify key model drivers of the revascularisation plus OMT vs OMT alone comparison. The impact of each variable on the ICER was explored. The top 10 drivers are presented visually using a tornado diagram (***Figure 58***). The major driver of the ICER was the risk ratio of all-cause mortality with revascularisation plus OMT vs OMT at 60 months.

Figure 58 Tornado diagram showing drivers of the ICER for revascularisation plus OMT vs OMT



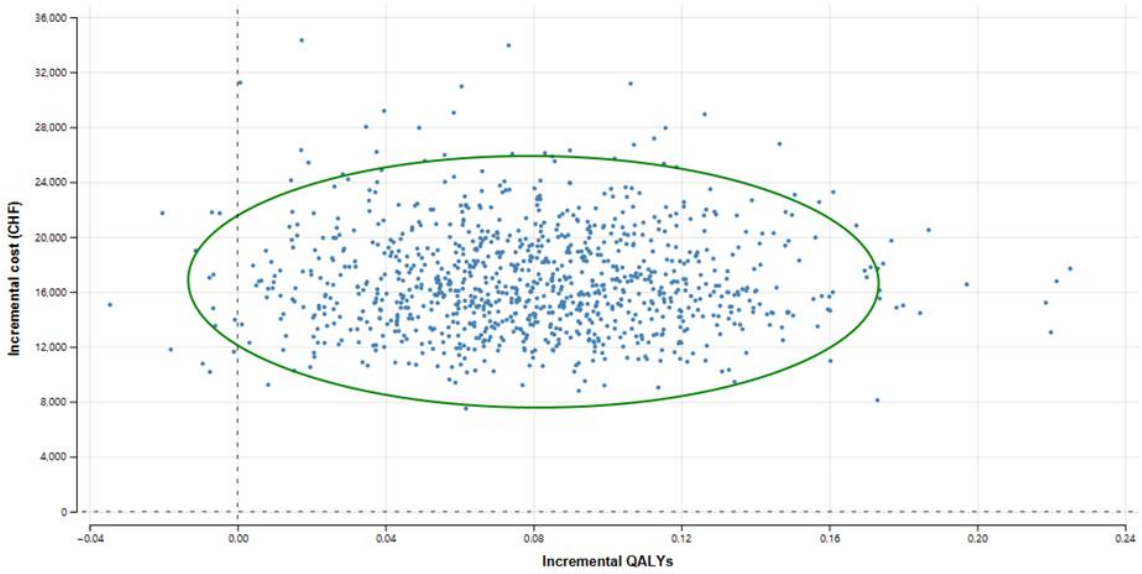
Abbreviations:
CABG: coronary artery bypass graft; **CHF**: Swiss franc; **DP**: disease perception (or quality of life) component score; **ICER**: incremental cost-effectiveness ratio; **mo**: months; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **PL**: physical limitations component score; **REV**: revascularisation; **RR**: risk ratio; **SAQ**: Seattle Angina Questionnaire; **TP**: transition probability; **TS**: treatment satisfaction component score.
Notes:
Blue and red bars represent lower and upper bounds of each parameter's uncertainty range, respectively. The numbers in brackets next to each parameter's description reflect the value of the lower and upper bounds for that parameter.

8.3.4.1.3 Probabilistic sensitivity analysis

To capture the joint uncertainty across model parameters, a PSA was undertaken to provide information to decision-makers on the overall certainty of the cost-effectiveness findings.

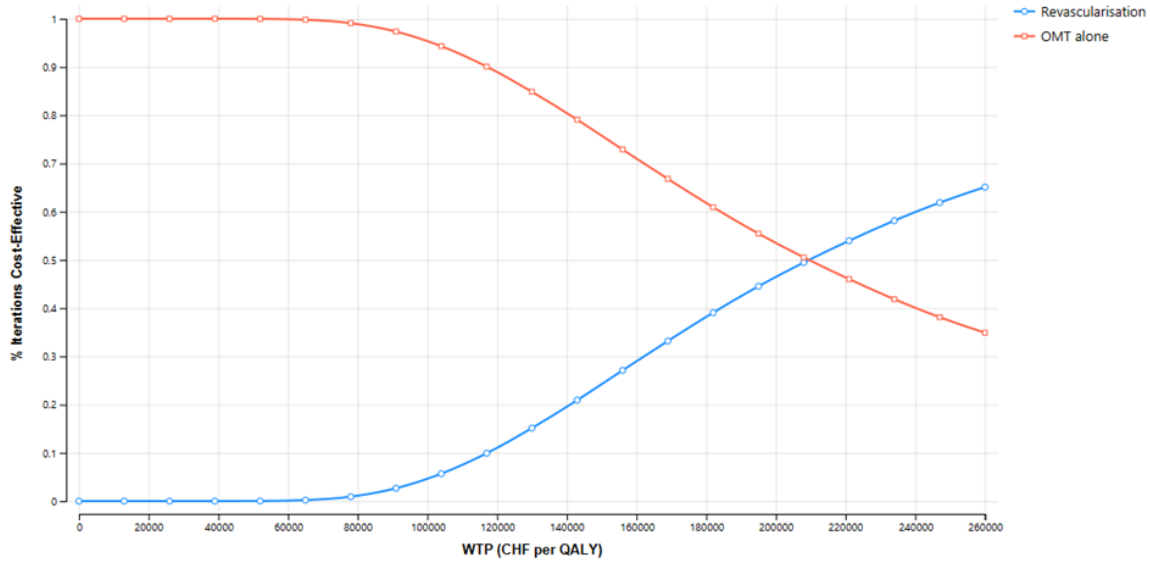
Most cost-effective pairs fall in the north-east quadrant of the cost-effectiveness plane (***Figure 59***). The probability that revascularisation plus OMT is cost effective relative to OMT exceeds 50% at and above a WTP threshold of approximately CHF210,000 (***Figure 60***).

Figure 59 Incremental cost-effect pairs for revascularisation plus OMT vs OMT



Abbreviations:
CHF: Swiss franc; **OMT**: optimal medical therapy; **QALY**: quality-adjusted life year; **REV**: revascularisation.

Figure 60 Cost-effectiveness acceptability curve for revascularisation plus OMT vs OMT



Abbreviations:
CHF: Swiss franc; **OMT**: optimal medical therapy; **QALY**: quality-adjusted life year; **REV**: revascularisation; **WTP**: willingness-to-pay.

8.3.4.1.4 ICER: chronic kidney disease subgroup analysis

The incremental cost-effectiveness of revascularisation plus OMT vs OMT alone using baseline event rates from the ISCHEMIA–CKD trial is presented in ***Table 34***. The CEAC curve for this scenario is presented in ***Appendix F***, ***Figure 68***. Revascularisation plus OMT was associated with higher expected per patient costs, life years and QALYs relative to OMT. ICERs of CHF253,224 and CHF106,276 were calculated over the 5-year and lifetime time horizons, respectively (***Table 34***). The probability that revascularisation plus OMT was the more cost-effective alternative exceeded 50% at and above a WTP threshold of just over CHF100,000 (***Figure 68***, ***Appendix F***).

Table 34 Incremental cost-effectiveness of revascularisation plus OMT vs OMT using alternative baseline event rates

	5-year horizon		Lifetime horizon (36 years)	
	Revascularisation + OMT	OMT alone	Revascularisation + OMT	OMT alone
Expected cost per patient (CHF)	24,705.68	7,486.96	31,386.58	13,913.58
Incremental cost (CHF)	17,218.72		17,473.00	
Expected Lys per patient	3.660	3.600	6.906	6.725
Incremental Lys	0.06		0.181	
Expected QALYs per patient	2.943	2.875	5.528	5.364
Incremental QALYs	0.068		0.164	
ICER (cost per QALY gained)	253,223.99		106,276.02	

Abbreviations:
CHF: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **LY**: life year; **OMT**: optimal medical therapy; **QALY**: quality-adjusted life year; **REV**: revascularisation.

8.3.4.1.5 Scenario analysis

Results of the scenario analyses are presented in ***Table 35***.

Table 35 Scenario analyses for revascularisation plus OMT vs OMT

Scenario	Incremental Cost (CHF)	Incremental QALY	ICER (CHF per QALY)
Base case	16,765.14	0.083	202,588.83
Discount rate: 0%	16,713.38	0.108	154,303.53
Discount rate: 6%	16,825.56	0.067	252,069.35
Alternative RR application[A]	16,672.89	0.029	576,102.88
Alternative RR application[A] with alternative extrapolation[B]	14,126.24	0.045	311,461.68

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year; **RR**: risk ratio.
Notes:
A: only statistically significant RR estimates for the MACE (at the longest timepoint for which a statistically significant effect was observed) were included.
B: only statistically significant RR estimates for MACE were included; and any significant treatment effects still present at last observed point of follow-up were extrapolated under the assumption of continuing treatment benefit.

8.3.4.2 Findings PCI plus OMT vs OMT

8.3.4.2.1 ICER

The incremental cost-effectiveness of PCI plus OMT vs OMT alone over 5-year (i.e. longest follow-up) and lifetime time horizons is presented in ***Table 36***. PCI plus OMT was associated with higher expected per patient costs but lower expected life years over both time horizons. In the short-term, PCI plus OMT was associated with higher QALYs, while over the longer-term this inverted (***Table 36***)—likely because PCI plus OMT was associated with significant short term improvements in patient HRQoL (modelled to attenuate after 12 months) and a non-significant increase in mortality (modelled over 5 years).

Table 36 Incremental cost-effectiveness of PCI plus OMT vs OMT

	5-year horizon		Lifetime horizon (36 years)	
	PCI + OMT	OMT alone	PCI + OMT	OMT alone
Expected cost per patient (CHF)	15,842.70	7,693.03	31,623.34	23,637.68
Incremental cost (CHF)	8,149.66		7,985.66	
Expected Lys per patient	4.410	4.443	13.485	13.612
Incremental Lys	-0.033		-0.127	
Expected QALYs per patient	3.570	3.566	10.858	10.936
Incremental QALYs	0.004		-0.078	
ICER (cost per QALY gained)	1.92 million		Dominated	

Abbreviations:
CHF: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **LY**: life year; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **QALY**: quality-adjusted life year.

8.3.4.2.2 Univariate sensitivity analysis

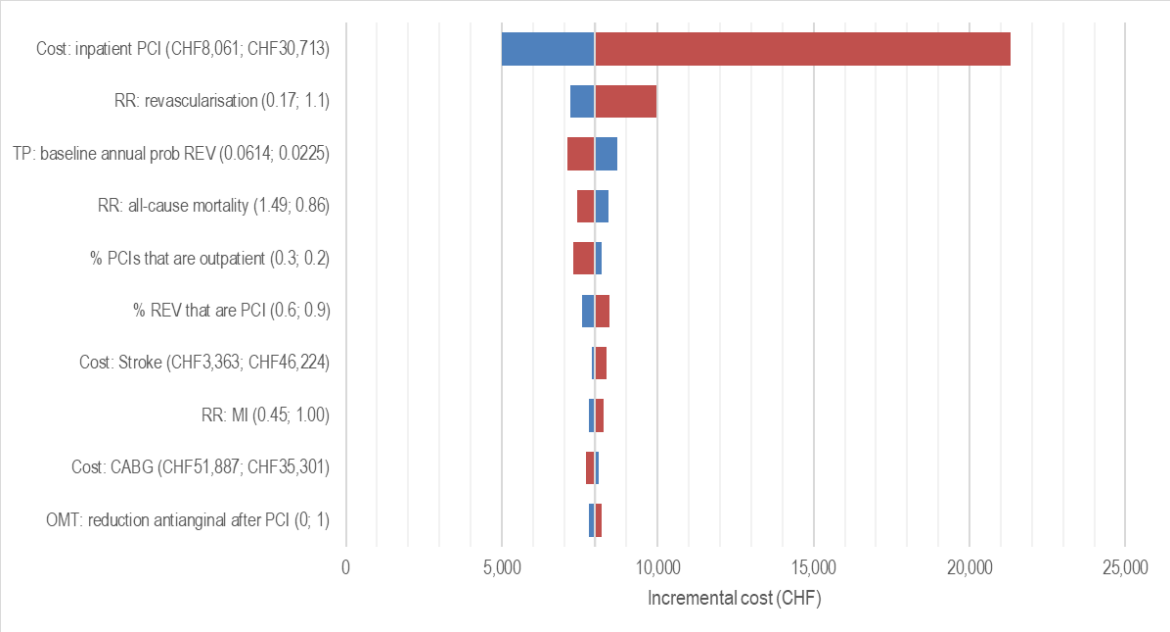
Univariate DSAs were used to identify key model drivers of the PCI plus OMT vs OMT comparison. Impacts of each variable on incremental costs and QALYs gained were explored separately given PCI plus OMT was dominated in the base-case evaluation. The top 10 drivers of each analysis are presented visually using tornado diagrams (***Figure 61*** and ***Figure 62***).

The major driver of incremental costs was the unit cost for an inpatient PCI procedure. This may be due to the large uncertainty range (CHF8,061 to CHF30,713; ***Section 8.3.1.1.1.1***). Other influential variables included the relative treatment effect of PCI plus OMT on subsequent revascularisation rates, the baseline transition probability for revascularisation in the OMT arm, and the relative treatment effect of PCI plus OMT on all-cause mortality (***Figure 61***).

The main driver of incremental QALYs was the relative treatment effect of PCI plus OMT with respect to all-cause mortality. Baseline all-cause mortality transition probability was the next most important driver, although its influence was far less pronounced than was the main driver (***Figure 62***).

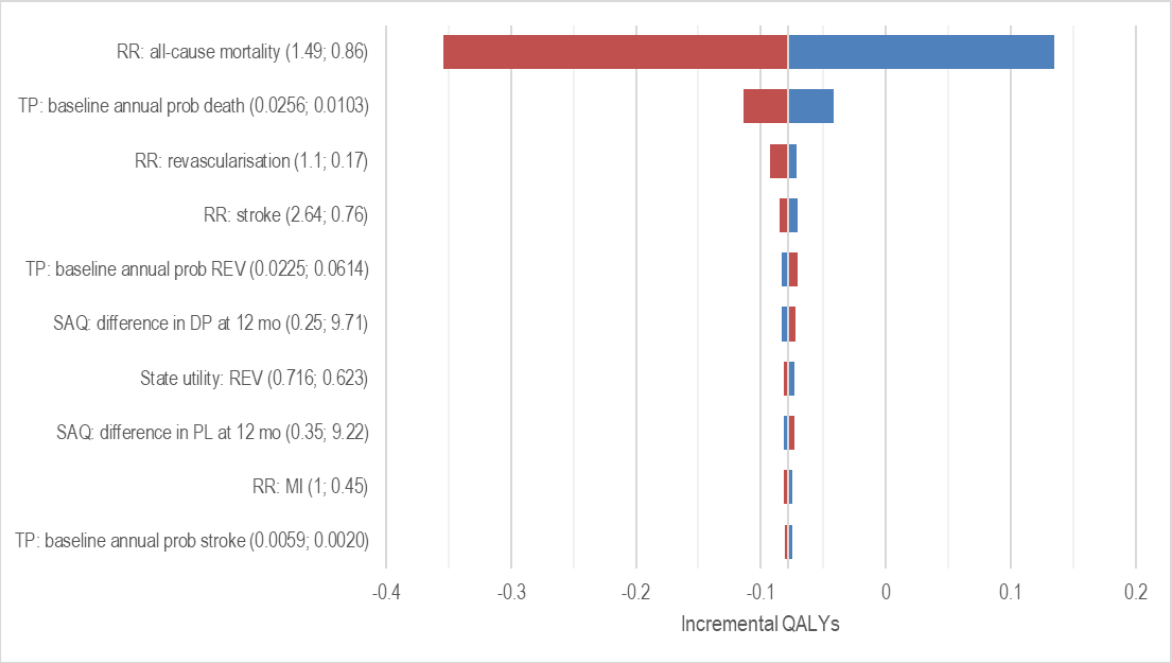
Considering the ICER (tornado diagram not shown), PCI remained dominated across the uncertainty ranges of all parameters except for one: the risk ratio of all-cause mortality with PCI plus OMT relative to OMT alone (RR: 1.13, 95% CI: 0.86 to 1.49). At the lower bound of this parameter, incremental QALYs inverted from negative to positive. This was associated with a shift in the ICER from the northwest quadrant of the cost-effectiveness plane, where PCI was dominated, to the northeast quadrant, with an associated ICER of CHF62,213.83.

Figure 61 Tornado diagram of incremental cost of PCI plus OMT vs OMT



Abbreviations:
CABG: coronary artery bypass surgery; **CHF**: Swiss franc; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **REV**: revascularisation; **RR**: risk ratio; **TP**: transition probability.
Notes:
Blue and red bars represent lower and upper bounds of each parameter's uncertainty range, respectively. The numbers in brackets next to each parameter's description reflect the value of the lower and upper bounds for that parameter.

Figure 62 Tornado diagram of incremental QALYs of PCI plus OMT vs OMT



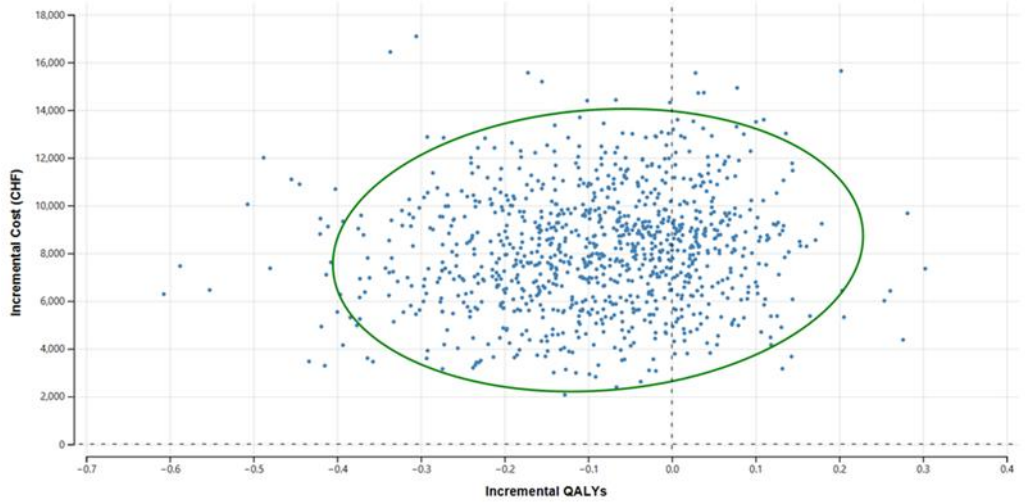
Abbreviations:
DP: disease perception (or quality of life) component score; **MI**: myocardial infarction; **mo**: months; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **PL**: physical limitations component score; **QALY**: quality-adjusted life year; **REV**: revascularisation; **RR**: risk ratio; **SAQ**: Seattle Angina Questionnaire: **TP**: transition probability.
Notes:
Blue and red bars represent lower and upper bounds of each parameter's uncertainty range, respectively. The numbers in brackets next to each parameter's description reflect the value of the lower and upper bounds for that parameter.

8.3.4.2.3 Probabilistic sensitivity analysis

Results of the PSA for comparison of PCI plus OMT vs OMT are presented as a 95% confidence ellipse on the cost-effectiveness plane (***Figure 63***) and as a CEAC (***Figure 64***).

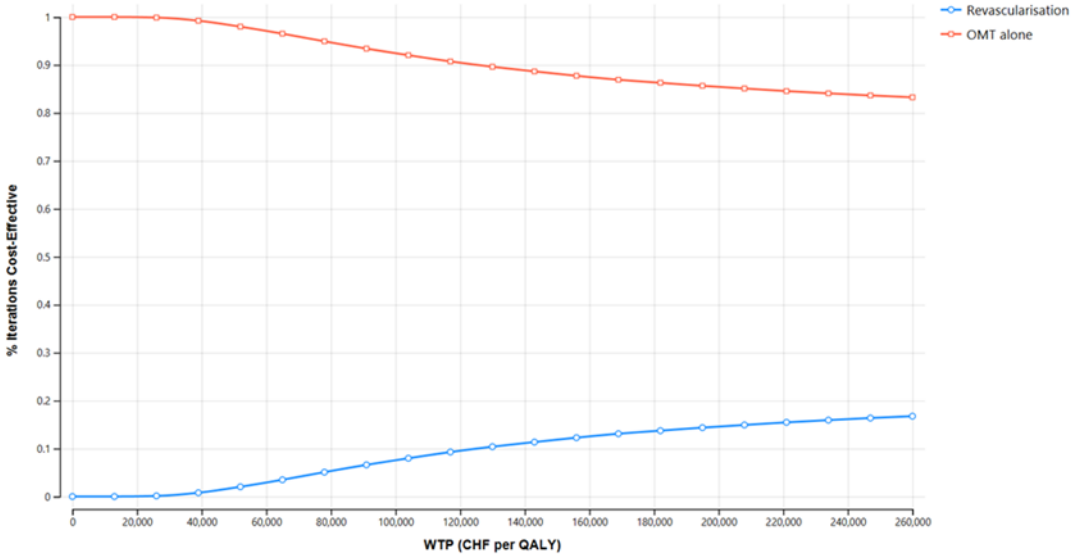
The cost-effect pairs lie across the north-west and north-east quadrants of the cost-effectiveness plane (***Figure 63***), suggesting there is certainty that PCI plus OMT is a more costly option than OMT but uncertainty regarding the direction of the incremental QALYs outcome (***Figure 63***). Nevertheless, the probability of PCI plus OMT being cost effective remains low (i.e. <20%) across all WTP thresholds (***Figure 64***).

Figure 63 Incremental cost-effect pairs for PCI plus OMT vs OMT



Abbreviations:
CHF: Swiss franc; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **QALY**: quality-adjusted life year.

Figure 64 Cost-effectiveness acceptability curve for PCI plus OMT vs OMT



Abbreviations:
CHF: Swiss franc; **OMT**: optimal medical therapy; **PCI:** percutaneous coronary intervention; **QALY**: quality-adjusted life year; **WTP**: willingness-to-pay.

8.3.4.2.4 ICER: FFR-guided PCI cohort subgroup analysis

The incremental cost-effectiveness of PCI plus OMT vs OMT using baseline event rates from the FAME 2 trial is presented in ***Table 37***. Like the base-case analysis, this analysis found PCI plus OMT to be associated with higher expected per patient costs but lower expected life years over both time horizons. Once again, in the short-term PCI plus OMT was associated with higher QALYs; this inverted over the longer-term (***Table 37***).

Table 37 Incremental cost-effectiveness of PCI plus OMT vs OMT using alternative baseline event rates

	5-year horizon		Lifetime horizon (36 years)	
	PCI + OMT	OMT alone	PCI + OMT	OMT alone
Expected cost per patient (CHF)	17,319.29	10,892.52	41,432.67	35,121.75
Incremental cost (CHF)	6,426.76		6,310.93	
Expected LYs per patient	4.490	4.505	14.483	14.568
Incremental LYs	-0.015		-0.085	
Expected QALYs per patient	3.629	3.604	11.607	11.635
Incremental QALYs	0.025		-0.029	
ICER (cost per QALY gained)	259,292.84		Dominated	

Abbreviations:
CHF: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **LY**: life year; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **QALY**: quality-adjusted life year.

8.3.4.2.5 Scenario analysis

Results of the scenario analyses for the PCI plus OMT vs OMT comparison are presented in ***Table 38***.

Table 38 Scenario analyses for PCI plus OMT vs OMT

Scenario	Incremental Cost (CHF)	Incremental QALY	ICER (CHF per QALY)
Base case	7,985.66	-0.078	PCI dominated
Discount rate: 0%	7,744.42	-0.121	PCI dominated
Discount rate: 6%	8,172.60	-0.051	PCI dominated
Alternative RR application[A]	8,982.65	0.20	443,709.88

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year; **RR**: risk ratio.
Notes:
A: only statistically significant RR estimates for the MACE events (at the longest timepoint for which a statistically significant effect was observed) were included.

8.3.4.2.6 Additional scenarios on extrapolation of HRQoL benefits

The clinical evidence suggests that PCI plus OMT (relative to OMT alone) is associated with significant improvements in SAQ component scores at 12 months for angina frequency, HRQoL and physical limitations (see ***Table 30***, ***Section 8.3.3.1.2***). However, PCI plus OMT (relative to OMT alone) was also associated with a non-significant increase in mortality risk (RR: 1.13, 95% CI: 0.86 to 1.49) (see ***Figure 10***, ***Section 7.4.3.2***). This may explain the positive incremental QALYs gained at 5 years but negative incremental LYs and incremental QALYs in the longer-term.

Given uncertainty in the true effect of PCI plus OMT on all-cause mortality, a scenario analysis was undertaken in which the RR model input was set equal to 1 from the beginning of the simulation. At all timepoints analysed in the clinical evaluation (i.e. 12, 24 and 60 months), the effect of PCI plus OMT relative to OMT alone on all-cause mortality was non-significant (***Figure 10***). This provides justification

for a scenario in which the RR of PCI plus OMT with respect to all-cause mortality is set equal to 1 for the duration of the simulation.

Additional scenarios were explored in which, in addition to the equivalent mortality rates, HRQoL benefits observed with PCI over 12 months were assumed to persist over 2 or 5 years. Results of these scenario analyses are presented in ***Table 39***.

When setting equivalent mortality rates across arms, the ICER inverted from PCI being dominated to CHF336,396.63. When, in addition, the HRQoL benefit was extrapolated to persist for 2- or 5-year periods, the ICER reduced further to CHF174,395.04 and CHF75,522.32, respectively.

Table 39 Incremental cost-effectiveness of PCI plus OMT vs OMT under scenario analyses on survival and HRQoL benefits

	ICER (CHF per QALY): Base case model	ICER (CHF per QALY): FAME 2-based model
Base case (lifetime)	PCI + OMT dominated	PCI + OMT dominated
RR for all-cause mortality set to 1 for the entire model horizon	336,395.63	167,989.19
HRQoL benefit extrapolated over 2 years	PCI + OMT dominated	PCI + OMT dominated
HRQoL benefit extrapolated over 5 years	1.30 million	114,870.60
RR for all-cause mortality set to 1 for the entire model horizon and HRQoL benefit extrapolated over 2 years	174,395.04	106,457.15
RR for all-cause mortality set to 1 for the entire model horizon and HRQoL benefit extrapolated over 5 years	75,522.32	52,942.12
Alternative RR application[A] and HRQoL benefit extrapolated over 2 years	209,061.68	156,312.60
Alternative RR application[A] and HRQoL benefit extrapolated over 5 years	86,815.14	71,738.14

Abbreviations:
CHF: Swiss franc; **FAME 2**: Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2; **HRQoL:** health-related quality of life; **ICER**: incremental cost-effectiveness ratio; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **QALY**: quality-adjusted life year; **RR**: risk ratio.
Notes:
A: only statistically significant RR estimates for the MACE events (at the longest timepoint for which a statistically significant effect was observed) were included.

8.3.4.3 Findings CABG plus OMT vs OMT

8.3.4.3.1 ICER

The incremental cost-effectiveness of CABG plus OMT vs OMT alone over 10-year (i.e. longest follow-up) and lifetime time horizons is presented in ***Table 40***. CABG plus OMT was associated with higher expected per patient costs, LYs and QALYs relative to OMT alone. ICERs of CHF290,735.12 and CHF173,065.27 were calculated over the 10-year and lifetime time horizons, respectively (***Table 40***).

Table 40 Incremental cost-effectiveness of CABG plus OMT vs OMT

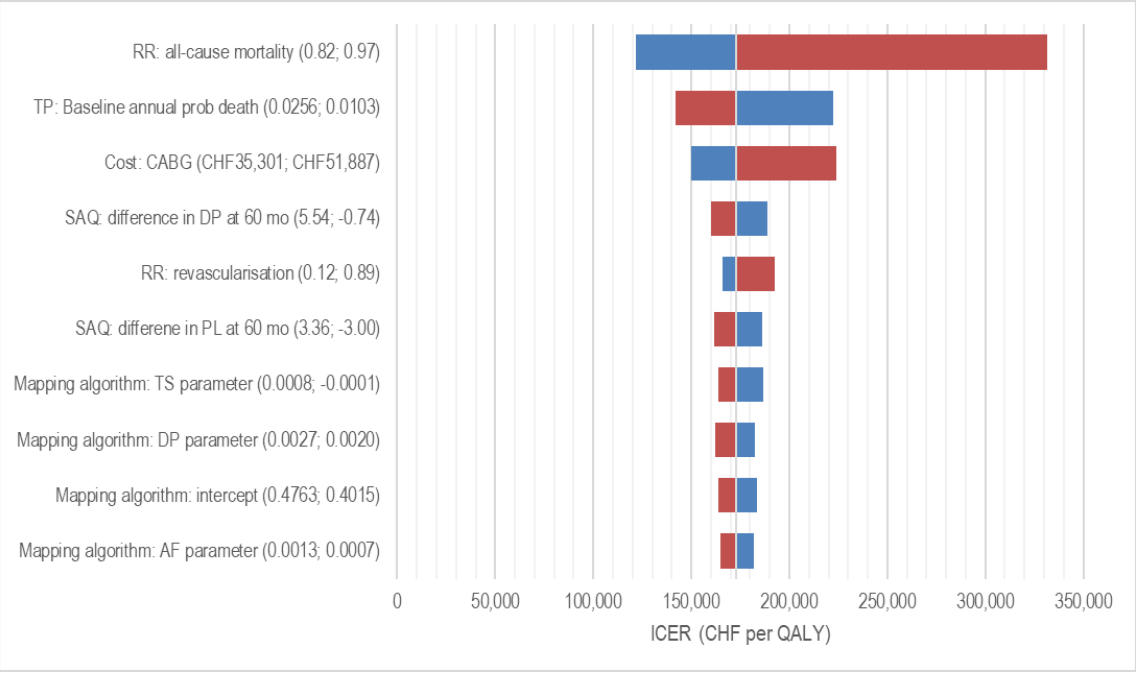
	10-year horizon		Lifetime horizon	
	CABG + OMT	OMT alone	CABG + OMT	OMT alone
Expected cost per patient (CHF)	51,341.28	13,341.28	61,596.87	23,637.68
Incremental cost (CHF)	37,761.88		37,959.19	
Expected LYs per patient	7.913	7.844	13.792	13.612
Incremental LYs	0.069		0.180	
Expected QALYs per patient	6.436	6.306	11.155	10.936
Incremental QALYs	0.130		0.219	
ICER (cost per QALY gained)	290,735.12		173,065.27	

Abbreviations:
CHF: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **LY**: life year; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **QALY**: quality-adjusted life year.

8.3.4.3.2 Univariate sensitivity analysis

Univariate DSAs were used to identify key model drivers of the CABG plus OMT vs OMT comparison. The impact of each variable on the ICER was explored, with the top 10 drivers presented visually using a tornado diagram (***Figure 65***). The major driver of the ICER was the RR of all-cause mortality with CABG plus OMT vs OMT at 120 months. Other important drivers included the baseline annual transition probability for death and the unit cost for CABG (***Figure 65***).

Figure 65 Tornado diagram showing drivers of the ICER for CABG plus OMT vs OMT

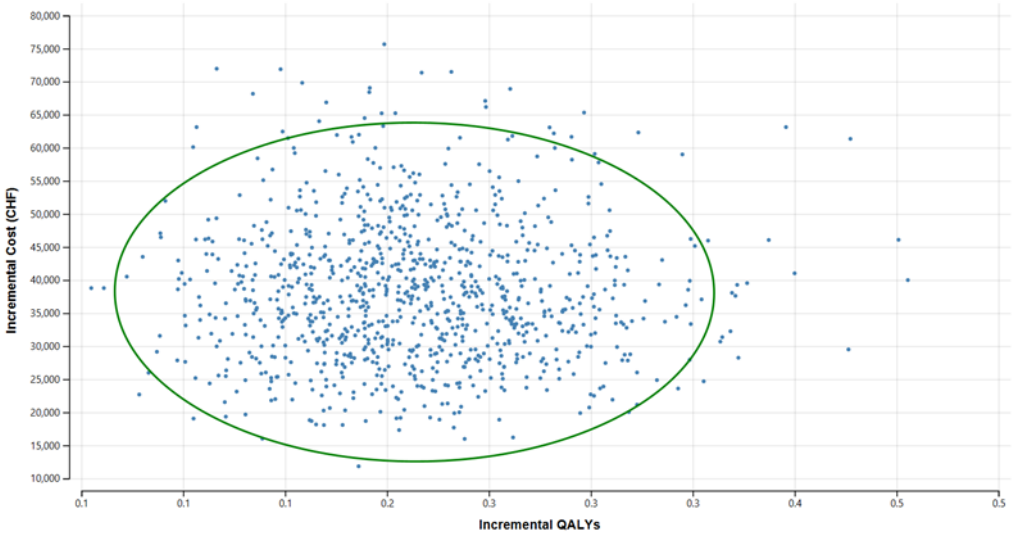


Abbreviations:
AF: angina frequency component score; **CABG**: coronary artery bypass graft; **CHF**: Swiss franc; **DP**: disease perception (or quality of life) component score; **ICER**: incremental cost-effectiveness ratio; **PL**: physical limitations component score; **QALY**: quality-adjusted life year; **RR**: risk ratio; **SAQ**: Seattle Angina Questionnaire; **TP**: transition probability; **TS**: treatment satisfaction component score.
Notes:
Blue and red bars represent lower and upper bounds of each parameter's uncertainty range, respectively. The numbers in brackets next to each parameter's description reflect the value of the lower and upper bounds for that parameter.

8.3.4.3.3 Probabilistic sensitivity analysis

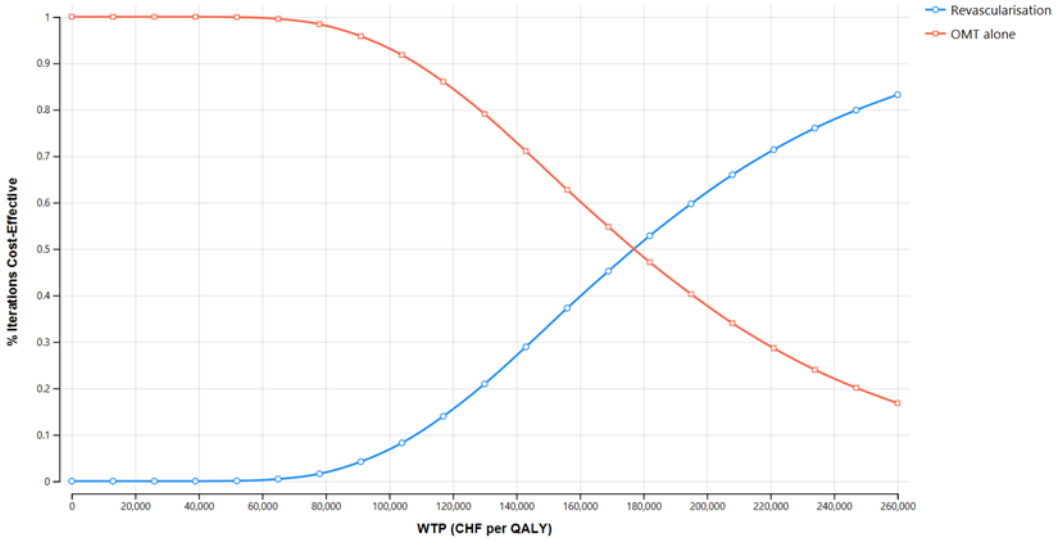
Results of the PSA are presented as a 95% confidence ellipse on the cost-effectiveness plane (***Figure 66***) and as a CEAC (***Figure 67***). All cost-effect pairs fall in the north-east quadrant of the cost-effectiveness plane (***Figure 66***). The probability that CABG plus OMT is cost effective relative to OMT alone exceeds 50% at and above a WTP threshold of approximately CHF180,000 (***Figure 67***).

Figure 66 Incremental cost-effect pairs for CABG plus OMT vs OMT



Abbreviations:
CABG: coronary artery bypass graft; **CHF**: Swiss franc; **OMT**: optimal medical therapy; **QALY**: quality-adjusted life year.

Figure 67 Cost-effectiveness acceptability curve for CABG plus OMT vs OMT



Abbreviations:
CABG: coronary artery bypass graft; **CHF**: Swiss franc; **OMT:** optimal medical therapy; **QALY**: quality-adjusted life year; **WTP**: willingness-to-pay.

8.3.4.3.4 ICER: reduced LVEF subgroup analysis

The incremental cost-effectiveness of CABG plus OMT vs OMT using baseline event rates from the STICH trial is presented in ***Table 41***. The CEAC curve for this scenario is presented in ***Appendix F***, ***Figure 69***.

CABG plus OMT was associated with higher expected per patient costs, LYs and QALYs relative to OMT alone. ICERs of CHF146,348.68 and CHF92,860.30 were calculated over the 10-year and lifetime time horizons, respectively (***Table 41***). The probability that CABG plus OMT was the more cost-effective alternative exceeded 50% at and above a WTP threshold of approximately CHF95,000 (***Appendix F, Figure 69***).

Table 41 Incremental cost-effectiveness of CABG plus OMT vs OMT using alternative baseline event risks

	10-year horizon		Lifetime horizon (36 years)	
	CABG + OMT	OMT alone	CABG + OMT	OMT alone
Expected cost per patient (CHF)	48,362.74	9,075.91	51,310.47	11,690.76
Incremental cost (CHF)	39,286.83		39,619.70	
Expected LYs per patient	5.684	5.426	7.449	6.993
Incremental LYs	0.258		0.456	
Expected QALYs per patient	4.608	4.339	6.016	5.590
Incremental QALYs	0.268		0.427	
ICER (cost per QALY gained)	146,347.68		92,860.30	

Abbreviations:
CABG: coronary artery bypass surgery; **CHF**: Swiss franc; **ICER**: incremental cost-effectiveness ratio; **LY**: life year; **OMT**: optimal medical therapy; **QALY**: quality-adjusted life year.

8.3.4.3.5 Scenario analysis

Results of the scenario analyses for CABG plus OMT vs OMT are presented in ***Table 42***.

Table 42 Scenario analyses for CABG plus OMT vs OMT

Scenario	Incremental Cost (CHF)	Incremental QALY	ICER (CHF per QALY)
Base case	37,959.19	0.219	173,065.27
Discount rate: 0%	37,842.31	0.296	127,800.42
Discount rate: 6%	38,098.51	0.172	221,331.15
Alternative RR application[A]	37,915.65	0.221	171,498.39
Alternative RR application[A] with alternative extrapolation[B]	33,363.09	0.324	102,853.57

Abbreviations:
CHF: Swiss francs; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year; **RR**: risk ratio.
Notes:
A: only statistically significant RR estimates for the MACE (at the longest timepoint for which a statistically significant effect was observed) were included.
B: only statistically significant RR estimates for MACE were included; and any significant treatment effects still present at last observed point of follow-up were extrapolated under the assumption of continuing treatment benefit.

8.3.4.4 Cross validation

To help readers judge the model's accuracy in making relevant predictions, cross validation exercises were undertaken (i.e. the model results were compared with the results of other studies).[183] Clinical outcomes such as LYs and QALYs provide a good point of comparison as there is generally less difference between evaluation contexts (e.g. due to differing currencies or thresholds).Therefore, these outcomes were considered for the cross validation. Findings of the existing evaluations are compared with the outcomes of the present evaluation in the discussion (***Section 11.1.2***).

8.3.4.4.1 CABG plus OMT vs OMT

The only identified cost-effectiveness study on CABG plus OMT was specific to patients with CCS and LVEF ≤35% (***Section 8.2.2.1***).[128] In its base case, this study assumed the mortality benefit observed with CABG plus OMT would persist beyond the 10-year follow-up. A scenario analysis in which the mortality benefit was assumed to attenuate after 10 years provides the best point of comparison with our modelling assumptions (i.e. any observed treatment effects would attenuate after longest follow-up). Expected per patient LYs and QALYs from the published scenario are compared with the subgroup analysis performed for this HTA for patients with CCS and LVEF ≤35% (***Table 43***).

Table 43 Cross validation of LY and QALY outcomes for CCS subgroup with LVEF ≤35%

	Chew 2022: scenario analysis with attenuated mortality benefit		Present evaluation: subgroup analysis for CCS patients with LVEF ≤35%	
	CABG + OMT[A]	OMT alone[A]	CABG + OMT	OMT alone
Expected LYs per patient	7.49 (6.69 to 8.42)	6.91 (6.36 to 7.55)	7.449	6.993
Incremental LYs	0.58 (0.09 to 1.08)		0.456	
Expected QALYs per patient	6.22 (5.56 to 6.98)	5.53 (5.08 to 6.06)	6.016	5.590
Incremental QALYs	0.69 (0.27 to 1.15)		0.427	

Abbreviations:
CABG: coronary artery bypass graft; **CCS**: chronic coronary syndrome; **LVEF**: left ventricular ejection fraction; **LY**: life year; **OMT**: optimal medical therapy; **QALY**: quality-adjusted life year.
Notes:
A: Results are reported as means with 95% confidence intervals.

8.3.4.4.2 PCI plus OMT vs OMT

Three identified cost-effectiveness studies on PCI plus OMT vs OMT sourced clinical outcome data from the FAME 2 RCT, including one model-based study that provides a good point of comparison with our model-based approach.[134] Expected per patient QALYs observed in the base case of the published study and the subgroup analyses (including additional scenarios for this subgroup) of the present evaluation are compared below (***Table 44***). LYs were not reported therefore a comparison across this metric was not possible.

Table 44 Cross validation of QALY outcomes for CCS subgroup with FFR ≤0.80

	Expected QALYs per patient		Incremental QALYs
	PCI + OMT	OMT alone	PCI + OMT vs OMT
Kodera 2019 (base case)[A]	12.73 (9.76 to 16.19)	12.60 (10.37 to 15.10)	0.13[B]
Present evaluation: subgroup analysis for patients with FFR ≤0.80			
Base case assumptions	11.607	11.635	-0.029
RR for all-cause mortality set to 1 for the entire model horizon	11.674	11.635	0.039
RR for all-cause mortality set to 1 for the entire model horizon and HRQoL benefit extrapolated over 5 years	11.758	11.635	0.123

Abbreviations:
FFR: fractional flow reserve; **HRQoL**: health-related quality of life; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **QALY**: quality-adjusted life year; **RR**: risk ratio.
Notes:
A: Results are reported as means with 95% confidence intervals.
B: Calculated based on the reported expected QALYs.

8.3.5 Findings: budget impact

Annual numbers of CABG and PCI procedures were estimated using a market share approach and extrapolated up to 2027. The budget impact of revascularisation over the period 2023 to 2027 was explored under current policy conditions.

8.3.5.1 Number of revascularisation procedures for CCS

8.3.5.1.1 Medstat data for CABG and PCI

Inpatient episode numbers according to the primary diagnosis code (ICD-10) and primary or secondary procedure codes (CHOP) over the period 2016 to 2020 are shown in ***Table 45***.

Notably, episode numbers for CABG have been reducing in recent years, while PCI numbers have been increasing (except for 2020) (***Table 45***). (The reduction in episode numbers in 2020 likely reflects an impact of the COVID-19 pandemic rather than practice trends.)

Table 45 Inpatient episode numbers according to diagnosis and surgical intervention codes

	2016	2017	2018	2019	2020
Diagnosis or procedure codes; numbers of claims					
Primary diagnosis code for CCS	9,458	9,643	10,269	10,635	9,262
Primary procedure code for CABG	2,672	2,708	2,549	2,499	2,238
Primary procedure code for PCI	15,202	15,669	16,813	17,394	15,484
Any procedure code for PCI [A]	20,232	20,977	22,081	22,641	20,583
Any procedure code for CABG [A]	3,707	2,708	2,549	2,499	2,238
Diagnosis AND procedure code combinations; numbers of claims					
Primary diagnosis code for CCS and primary procedure code for CABG	1,756	1,728	1,677	1,589	1,435
Primary diagnosis code for CCS and primary procedure code for PCI	6,496	6,751	7,513	8,035	6,722
Primary diagnosis code for CCS and any procedure code for CABG [A]	1,932	1,851	1,791	1,721	1,549
Primary diagnosis code for CCS and any procedure code for PCI [A]	7,531	7,810	8,500	8,925	7,435

Abbreviations:
CABG: coronary artery bypass graft; **CCS**: chronic coronary syndrome; **DRG**: diagnosis-related group; **PCI**: percutaneous coronary intervention.
Notes:
A: Primary or secondary procedure code.
Source:
MedStat database.[156]

8.3.5.1.2 TARMED data (PCI only)

Annual claims numbers for TARMED position 17.1110 over the period 2016 to 2021 are shown in ***Table 46***. Numbers of claims for this position have trended upward over the period, despite the COVID-19 pandemic.

Table 46 TARMED claims numbers for PTCA

		2016	2017	2018	2019	2020	2021
17.1110	PTCA for coronary stenoses or coronary occlusions, first dilated vascular segment	4,664	5,103	4,599	5,613	5,944	6,892

Abbreviations:
PTCA: percutaneous transluminal coronary angioplasty.
Source:
Tarifpool © SASIS AG.

8.3.5.1.3 Swiss PCI survey

Data collected annually by the Interventional Cardiology Working Group of the Swiss Society of Cardiology provide information on the number of diagnostic and interventional percutaneous cardiac procedures (including PCI) performed annually at Swiss interventional cardiology centres.[33,149,184] This dataset contains information on indications for intervention, including whether PCI was performed as an emergency procedure (i.e. for non-ST-elevation ACS, ST-elevation MI or cardiogenic shock).[33,149,184]

Reported numbers of PCI procedures and the percentages that were emergency cases for 2018 to 2020 are shown in ***Table 47***.[33,149,184] Numbers of non-emergency PCI cases were derived (***Table 47***). While a reduction in the number of PCIs was observed between 2019 and 2020, this reflects the impact of the COVID-19 pandemic rather than reduced utilisation of the technology in practice.[184]

Table 47 Annual number of non-emergency PCI procedures from the Swiss PCI survey

	2018	2019	2020	2021
PCI (total)	27,318	27,959	25,933	26,513
Emergency PCI (%)	40.4%	42%	39%	44%
Non-emergency PCI (total)	16,282	16,216	15,819	14,847

Abbreviations:
PCI: percutaneous coronary intervention.
Notes:
Emergency PCIs include those for non-ST-elevation ACS, ST-elevation MI and cardiogenic shock.
For 2018, individual reported percentages for non-ST-elevation ACS, ST-elevation MI and cardiogenic shock were combined to provide an overall estimate.
Data shown in red were identified after completion of the draft HTA.
Source:
Swiss Working Group for Interventional Cardiology annual survey of invasive diagnostic and therapeutic heart interventions results.[33,149,184,185]

These numbers were not used in the base-case analysis but did inform the upper limit of annual PCI procedures in a sensitivity analysis (***Section 8.3.5.5.3***).

After completion of the draft HTA, Swiss PCI survey data for 2021 were subsequently published (December 2022).[185] According to the additional data, 26,513 PCIs were performed in Switzerland in 2021, of which 56% were for CCS (i.e. non-emergency procedures; ***Table 47***). Authors found COVID-19 had only a minor impact on PCI in Switzerland; the peak in PCI numbers occurred in 2019 (before the pandemic).[185] The proportion of emergency PCIs increased between 2018 and 2021, except for 2020 during the peak of the pandemic (***Table 47***). Additional scenario analyses were added taking into account these additional data.

8.3.5.2 Observed trends in the use of revascularisation for CCS

Observed trends in the use of revascularisation procedures over the period 2016 to 2020, based on MedStat and TARMED episode numbers, are presented in ***Table 48***.

Diagnosis-related information is unavailable in TARMED, so an assumption was made about the proportion of claims for CCS patients. It was assumed that the proportion of PCIs for CCS relative to all PCIs (primary procedure codes only) observed in annual inpatient episodes would reflect the proportion of outpatient PCIs performed for CCS. Proportions based on Medstat data were derived per annum. Conservatively, the highest observed rate (46.2% in 2019) was adopted.

TARMED data were available for 2021 but Medstat data were not, so 2021 was included within the extrapolation period for inpatient case numbers (see ***Section 8.3.5.3***).

Table 48 Assumed CABG and PCI numbers for patients with CCS

	Parameter	2016	2017	2018	2019	2020	2021	Trend	Cross Ref
	CABG								
A	CABG: total	1,932	1,851	1,791	1,721	1,549	NR	Decreasing (–3.8% p.a.) [A]	***Table 45***
	PCI								
B	PCI: inpatient	7,531	7,810	8,500	8,925	7,435	NR	Increasing (5.8% p.a.) [B]	**Table 45**
C	PCI: outpatient	2,154	2,357	2,124	2,593	2,746	3,184	Increasing (8.1% p.a.)	**Table 46** * 0.462 [C]
D	PCI: total	9,685	10,167	10,624	11,518	10,181	NE	Increasing (5.9% p.a.)	B + C

Abbreviations:
CABG: coronary artery bypass graft; **CCS**: chronic coronary syndrome; **NE**: not estimable; **NR**: not reported; **p.a.**: per annum; **PCI:** percutaneous coronary intervention.
Notes:
A: Trend calculation excludes the year 2020, given the potential influence of the COVID-19 pandemic.
B: Trend calculation excludes the year 2020. Between 2019 and 2020 there was a decline of 16.7%; however, this is likely an anomaly attributable to the COVID-19 pandemic.
C: Proportion of PCI (primary procedure code only) for CCS relative to all PCIs (primary procedure code only) observed in Swiss DRG annual episode numbers. Conservatively, the highest observed percentage—for the year 2019—was adopted.

8.3.5.3 Projected number of revascularisation procedures for CCS

Extrapolated numbers of CABG and PCI (inpatient and outpatient considered separately) procedures for patients with CCS are presented in ***Table 49***.

Table 49 Extrapolated CABG and PCI numbers for patients with CCS

Parameter	2021	2022	2023	2024	2025	2026	2027	Extrapolation
CABG								
CABG: total	1,593	1,533	1,475	1,419	1,366	1,314	1,264	–3.8% p.a. from 2019 figure
PCI								
PCI: inpatient	9,995	10,577	11,193	11,845	12,535	13,265	14,037	5.8% p.a. from 2019 figure
PCI: outpatient	3,184 [A]	3,442	3,722	4,024	4,351	4,705	5,087	8.1% p.a. from 2021 figure
PCI: total	11,052	11,769	12,533	13,349	14,219	15,147	16,137	NA

Abbreviations:
CABG: coronary artery bypass graft; **CCS**: chronic coronary syndrome; **NA**: not applicable; **p.a.**: per annum; **PCI**: percutaneous coronary intervention.
Notes:
Extrapolation of inpatient procedure number began from 2019 rather than 2020; 2020 estimates were excluded from the analysis due to the potential impact of the COVID-19 pandemic on patient numbers.
A: This figure based on actual claims data, not an extrapolation.

8.3.5.4 Projected costs of revascularisation procedures for CCS

Projected revascularisation procedure costs were derived using the procedure costs described in ***Section 8.3.1.1*** (***Table 13***, ***Table 14*** and ***Table 15***).

Table 50 Projected cost of revascularisation procedures in patients with CCS

	Parameter	2023	2024	2025	2026	2027	Calculation
	CABG						
A	CABG: total	59.7M	57.4M	55.3M	53.2M	51.2M	***Table 49*** * CHF40,459.52
	PCI						
B	PCI: inpatient	136.7M	144.7M	153.1M	162.1M	171.5M	***Table 49*** * CHF12,216.93
C	PCI: outpatient	9.4M	10.1M	11.0M	11.9M	12.8M	***Table 49*** * CHF2,520.98
D	PCI: total	146.1M	154.9M	164.1M	173.9M	184.3M	B + C

Abbreviations:
CABG: coronary artery bypass graft; **CCS**: chronic coronary syndrome; **CHF:** Swiss franc; **M**: million; **PCI**: percutaneous coronary intervention.

8.3.5.5 Sensitivity analysis

Some of the key assumptions used in the budget impact analysis are uncertain or variable, including estimated annual numbers of revascularisation procedures for CCS patients, assumed growth in annual procedure numbers and cost per procedure. Alternative assumptions regarding these parameters were explored in sensitivity and scenario analyses. In the sensitivity analysis, input parameters in question were varied across an assumed uncertainty range. Scenario analyses explored the impact of the chosen methods or assumptions on the budget estimates.

Overall, anticipated payer costs for CABG were estimated at ranging between CHF46.0 million and CHF56.3 million in 2027; anticipated payer costs for PCI were estimated at ranging between CHF143.7 million and CHF201.5 million.

8.3.5.5.1 Sensitivity analysis: projected CABG costs

DRG codes for CABG are not specific to the indication of CCS. The number of procedures for the indication of interest were derived based on diagnosis and procedure codes, which introduces some uncertainty into the estimate. When the derived number of procedures for 2019 (used as the basis for future extrapolations) was varied by ±10%, estimated payer costs varied between CHF46.0 million and CHF56.3 million in 2027 (***Table 51***).

The rate of change in CABG procedure numbers was assumed based on recent trends; however, it is uncertain how closely future trends will align with historic trends. When the assumed annual rate of

change was varied by ±20%, estimated payer costs varied between CHF48.0 million and CHF54.5 million in 2027 (***Table 51***).

Finally, the future cost for CABG procedures remains unknown. When the assumed mean cost per procedure was varied by ±10%, estimated payer costs varied between CHF46.0 million and CHF56.3 million in 2027 (***Table 51***).

Table 51 Sensitivity analyses on projected CABG payer costs

	Scenario	2023	2024	2025	2026	2027	Calculation
	Base case						
A	Procedures	1,475	1,419	1,366	1,314	1,264	***Table 49***
B	Payer costs (CHF)	59.7M	57.4M	55.3M	53.2M	51.2M	***Table 50***
	Estimated procedure numbers for 2019 (-10%)						
C	Procedures	1,328	1,277	1,229	1,183	1,138	–3.8% p.a. from 1,549 in 2019
D	Payer costs (CHF)	53.7M	51.9M	49.7M	47.8M	46.0M	C * CHF40,460
	Estimated procedure numbers for 2019 (+10%)						
E	Procedures	1,623	1,561	1,502	1,445	1,391	–3.8% p.a. from 1,893 in 2019
F	Payer costs (CHF)	65.6M	63.2M	60.8M	58.5M	56.3M	E * CHF40,460
	Assumed growth rate (-20%)						
G	Procedures	1,522	1,476	1,431	1,388	1,346	–3.0% p.a. from 2019 figure
H	Payer costs (CHF)	61.6M	59.7M	57.9M	56.2M	54.5M	G * CHF40,460
	Assumed growth rate (+20%)						
I	Procedures	1,429	1,364	1,302	1,243	1,187	–4.6% p.a. from 2019 figure
J	Payer costs (CHF)	57.8M	55.2M	52.7M	50.3M	48.0M	I * CHF40,460
	Unit cost CABG (-10%)						
K	Payer costs (CHF)	53.7M	51.7M	49.7M	47.8M	46.0M	A * CHF32,368
	Unit cost CABG (+10%)						
L	Payer costs (CHF)	65.6M	63.2M	60.8M	58.5M	56.3M	A * CHF:48,551

Abbreviations:
CABG: coronary artery bypass graft; **CHF:** Swiss franc; **M:** million; **p.a.:** per annum.

8.3.5.5.2 Sensitivity analysis: projected PCI costs

DRG codes for PCI are not specific to the indication of CCS. The number of procedures for the indication of interest was derived based on diagnosis and procedure codes, which introduces some uncertainty into the estimate. When the derived number of procedures for 2019 (used as the basis for future extrapolations) was varied by ±10%, estimated payer costs varied between CHF167.2 million and CHF201.5 million in 2027 (***Table 52***).

The number of outpatient PCIs for CCS was estimated based on 2 assumptions: (1) claims numbers for TARMED position 17.1110 reflect the number of outpatient PCI procedures, and (2) the proportion of inpatient PCI procedures for CCS (vs indications) reflects the proportion of outpatient procedures for CCS also. This reliance on assumptions introduces uncertainties to the analysis. When the assumed number of procedures for 2021 (used as the basis for future extrapolations) was varied by ±20%, estimated payer costs varied between CHF181.8 million and CHF186.9 million in 2027 (***Table 52***).

The rate of change in PCI procedure numbers was assumed based on recent trends; however, it is uncertain how closely future trends will align with historic trends. When the assumed annual rate of growth in the number of inpatient PCI procedures was varied by ±20%, estimated payer costs varied between CHF169.8 million and CHF200.0 million in 2027 (***Table 52***). When the assumed annual rate of growth in the number of outpatient PCI procedures was varied by 20%, estimated payer costs varied between CHF183.2 million and CHF185.5 million (***Table 52***).

Future costs for PCI procedures remain unknown. When the assumed mean cost per inpatient procedure was varied by ±10%, estimated payer costs varied between CHF167.2 million and CHF201.5 million (***Table 52***). When the assumed mean cost per outpatient procedure was varied by ±20%, estimated payer costs varied between CHF181.8 million and CHF186.9 million (***Table 52***).

Table 52 Sensitivity analyses on projected PCI payer costs

	Scenario	2023	2024	2025	2026	2027	Calculation
	Base case						
A	Procedures; inpatient	11,193	11,845	12,535	13,265	14,037	***Table 49***
B	Procedures; outpatient	3,722	4,024	4,351	4,705	5,087	***Table 49***
C	Procedures; total	14,915	15,869	16,886	17,970	19,124	***Table 49***
D	Payer costs (CHF); inpatient	136.7M	144.7M	153.1M	162.1M	171.5M	***Table 50***
E	Payer costs (CHF); outpatient	9.4M	10.1M	11.0M	11.9M	12.8M	***Table 50***
F	Payer costs (CHF); total	146.1M	154.9M	164.1M	173.9M	184.3M	***Table 50***
	Estimated procedure numbers inpatient PCI for 2019 (-10%)						
G	Procedures; inpatient	10,074	10,660	11,281	11,938	12,634	5.8% p.a. from 8,033 in 2019
H	Payer costs (CHF); inpatient	123.1M	130.2M	137.8M	145.9M	154.3M	G * CHF12,217
I	Payer costs (CHF); total	132.5M	140.4M	148.8M	157.7M	167.2M	H + E
	Estimated procedure numbers inpatient PCI for 2019 (+10%)						
J	Procedures; inpatient	12,312	13,029	13,788	14,591	15,441	5.8% p.a. from 9,818 in 2019
K	Payer costs (CHF); inpatient	150.4M	159.2M	168.5M	178.3M	188.6M	J * CHF12,217
L	Payer costs (CHF); total	159.8M	169.3M	179.4M	190.1M	201.5M	K + E
	Estimated procedure numbers outpatient PCI for 2021 (-20%)						
M	Procedures; outpatient	2,978	3,219	3,481	3,764	4,069	8.1% p.a. from 2,547 in 2021
N	Payer costs (CHF); outpatient	7.5M	8.1M	8.8M	9.5M	10.3M	M * CHF2,521

	Scenario	2023	2024	2025	2026	2027	Calculation
O	Payer costs (CHF); total	144.3M	152.8M	161.9M	171.5M	181.8M	N + D
	Estimated procedure numbers outpatient PCI for 2021 (+20%)						
P	Procedures; inpatient	4,466	4,829	5,221	5,646	6,104	8.1% p.a. from 3,820 in 2021
Q	Payer costs (CHF); outpatient	11.3M	12.2M	13.2M	14.2M	15.4M	P * CHF2,521
R	Payer costs (CHF); total	148.0M	156.9M	166.3M	176.3M	186.9M	Q + D
	Assumed growth rate inpatient PCI (-20%)						
S	Procedures; inpatient	10,708	11,207	11,729	12,276	12,848	4.7% from 2019 figure
T	Payer costs (CHF); inpatient	130.8M	136.9M	143.3M	150.0M	157.0M	S * CHF12,217
U	Payer costs (CHF); total	140.2M	147.1M	154.3M	161.8M	169.8M	T + E
	Assumed growth rate inpatient PCI (+20%)						
V	Procedures; inpatient	11,694	12,511	13,386	14,321	15,322	7.0% from 2019 figure
W	Payer costs (CHF); inpatient	142.9M	152.9M	163.5M	175.0M	187.2M	V * CHF12,217
X	Payer costs (CHF); total	152.2M	163.0M	174.5M	186.8M	200.0M	W + E
	Assumed growth rate outpatient PCI (-20%)						
Y	Procedures; outpatient	3,611	3,846	4,095	4,362	4,645	6.5% from 2021 figure
Z	Payer costs (CHF); outpatient	9.1M	9.7M	10.3M	11.0M	11.7M	Y * CHF2,521
AA	Payer costs (CHF); total	145.8M	154.4M	163.5M	173.1M	183.2M	Z + D
	Assumed growth rate outpatient PCI (+20%)						
BB	Procedures; outpatient	3,835	4,208	4,619	5,069	5,563	9.7% from 2021 figure
CC	Payer costs (CHF); outpatient	9.7M	10.6M	11.6M	12.8M	14.0M	BB* CHF2,521
DD	Payer costs (CHF); total	146.4M	155.3M	164.8M	174.8M	185.5M	CC + D
	Unit cost inpatient PCI (-10%)						
EE	Payer costs (CHF); inpatient	123.1M	130.2M	137.8M	145.9M	154.3M	A * CHF9,774
FF	Payer costs (CHF); total	132.5M	140.4M	148.8M	157.7M	167.2M	FF + E
	Unit cost inpatient PCI (+10%)						
GG	Payer costs (CHF); inpatient	150.4M	159.2M	168.5M	178.3M	188.6M	A * CHF14,660
HH	Payer costs (CHF); total	159.8M	169.3M	179.4M	190.1M	201.5M	GG + E
	Unit cost outpatient PCI (-20%)						
II	Payer costs (CHF); outpatient	7.5M	8.1M	8.8M	9.5M	10.3M	B * CHF2,017
JJ	Payer costs (CHF); total	144.3M	152.8M	161.9M	171.5M	181.8M	II + D
	Unit cost outpatient (+20%)						
KK	Payer costs (CHF); outpatient	11.3M	12.2M	13.2M	14.2M	15.4M	B * CHF3,025
LL	Payer costs (CHF); total	148.0M	156.9M	166.3M	176.3M	186.9M	KK + D

Abbreviations:

CHF: Swiss franc; **M:** million; **PCI**: percutaneous coronary intervention.

8.3.5.5.3 Scenario analysis: PCI patient numbers

PCI numbers informing this scenario were derived from data reported as part of the annual Swiss PCI survey (***Section 8.3.5.1.3***). Annual numbers of PCI procedures were extrapolated based on the growth in PCI numbers between 2018 and 2019 (i.e. 2.3% p.a.). (Data from 2020 were not included in the calculations due to the potential impact of the COVID-19 pandemic on PCI numbers, therefore PCI numbers were extrapolated from 2019 onwards.)

The percentage of total PCIs performed for patients with CCS was assumed to be 46.2%, based on the proportion of PCIs for CCS relative to all PCIs (primary procedure codes) observed in Swiss DRG episode numbers for 2019.

The percentage of PCIs for CCS performed in the outpatient setting was assumed to be 22.4% in 2020, based upon the proportion of outpatient PCIs (i.e. claims for TARMED position 17.1110) relative to the total number of PCIs (i.e. claims for TARMED position 17.1110 plus DRG episodes with a PCI-related procedure code). This proportion was assumed to increase to 30.7% in 2027 (from extrapolations based on the observed trend between 2016 and 2020). In an alternative assumption this proportion was instead held constant at 22.4%.

Under the scenario assuming increased relative use of outpatient PCIs, payer costs were estimated at CHF143.7 million in 2027 (***Table 53***). In the scenario assuming no increase in outpatient procedures, payer costs were estimated at CHF156.2 million in 2027 (***Table 53***).

Table 53 Scenario analyses on projected PCI payer costs

	Parameter	2023	2024	2025	2026	2027	Calculation
	PCI numbers						
A	PCIs total	30,677	31,397	32,134	32,887	33,659	Extrapolated based on data from ***Table 47***
B	PCIs for CCS	14,171	14,503	14,844	15,192	15,549	A * 46.2% [A]
	Scenario 1						
C	Inpatient PCIs	10,539	10,616	10,683	10,739	10,782	B – D
D	Outpatient PCIs	3,632	3,887	4,160	4,453	4,766	B * 25.6–30.7%; dependent on year [B]
	Scenario 2						
E	Inpatient PCIs	10,996	11,254	11,518	11,788	12,065	B – F
F	Outpatient PCIs	3,175	3,250	3,326	3,404	3,484	B * 22.4% [C]
	PCI costs (CHF): Scenario 1						
G	Cost inpatient	128.8M	129.7M	130.5M	131.2M	131.7M	C * CHF12,217
H	Cost outpatient	9.2M	9.8M	10.5M	11.2M	12.0M	D * CHF2,521
I	TOTAL COST (PCI)	137.9M	139.5M	141.0M	142.4M	143.7M	G + H
	PCI costs (CHF): Scenario 2						
J	Cost inpatient	134.3M	137.5M	140.7M	144.0M	147.4M	E * CHF12,217
K	Cost outpatient	8.0M	8.2M	8.4M	8.6M	8.8M	F * CHF2,521
L	TOTAL COST (PCI)	142.3M	145.7M	149.1M	152.6M	156.2M	J + K

Abbreviations:
CCS: chronic coronary syndrome; **CHF**: Swiss franc; **M:** million; **PCI**: percutaneous coronary intervention.
Notes:
A: The figure 46.2% reflects the proportion of PCIs for CCS relative to all PCIs (primary procedure codes) observed in Swiss DRG episode numbers for 2019.
B: Figures were derived by extrapolating the relative proportion of outpatient to total PCI procedures for 2016–2020 over the 2021–2027 period.
C: The figure 22.4% reflects the proportion of outpatient PCIs (TARMED claims) relative to all PCIs (TARMED and DRG claims) for the year 2020.

PCI survey data for 2021, published after completion of the draft HTA, suggest COVID-19 had a limited impact on PCI in Switzerland, a peak in PCI numbers were reached in 2019, and the proportion of PCIs performed for emergency cases is increasing (i.e. proportion performed for CCS may be decreasing; ***Section 8.3.5.1.3***).[185] The overall trend in PCIs for CCS based on these data (16,282 and 14,847 non-emergency procedures in 2018 and 2021, respectively, ***Table 47***) reflects an annual decline of 3.0%.

Scenario analyses based on an extrapolation of PCI for CCS numbers using an annual decline of 3.0% on 14,847 procedures in 2021 are also presented (***Table 54***). Under the scenario assuming increased relative use of outpatient PCIs, payer costs were estimated at CHF114.1 million in 2027. In the scenario assuming no increase in outpatient procedures, payer costs were estimated at CHF124.0 million in 2027.

Table 54 Additional scenario analyses on projected PCI payer costs

	Parameter	2023	2024	2025	2026	2027	Calculation
	PCI numbers						
A	PCIs for CCS	13,962	13,539	13,130	12,732	12,347	–3.0% p.a. from 2021 figure of 14,847 (***Table 47***)
	Scenario 1						
B	Inpatient PCIs	10,384	9,911	9,450	9,000	8,562	A – C
C	Outpatient PCIs	3,578	3,629	3,680	3,732	3,785	A * 25.6–30.7%; dependent on year [A]
	Scenario 2						
D	Inpatient PCIs	10,833	10,506	10,188	9,879	9,580	A – E
E	Outpatient PCIs	3,129	3,034	2,942	2,853	2,767	A * 22.4% [B]
	PCI costs (CHF): Scenario 1						
F	Cost inpatient	126.9M	121.1M	115.4M	110.0M	104.6M	B * CHF12,217
G	Cost outpatient	9.02M	9.15M	9.28M	8.41M	9.54M	C * CHF2,521
H	TOTAL COST (PCI)	135.9M	130.2M	124.7M	119.4M	114.1M	F + G
	PCI costs (CHF): Scenario 2						
I	Cost inpatient	132.4M	128.3M	124.5M	120.7M	117.0M	D * CHF12,217
J	Cost outpatient	7.89M	7.65M	7.42M	7.19M	6.97M	E * CHF2,521
K	TOTAL COST (PCI)	140.2M	136.0M	131.9M	127.9M	124.0M	I + J

Abbreviations:

CCS: chronic coronary syndrome; **CHF**: Swiss franc; **M:** million; **PCI**: percutaneous coronary intervention.

Notes:

A: Figures were derived by extrapolating the relative proportion of outpatient to total PCI procedures for 2016–2020 over the 2021–2027 period.

B: The figure 22.4% reflects the proportion of outpatient PCIs (TARMED claims) relative to all PCIs (TARMED and DRG claims) for the year 2020.

9 Ethical, legal, social and organisational issues

Summary statement: ethical, legal, social and organisational issues

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The literature searches identified 10 publications related to ethical, social and organisational issues associated with using PCI, CABG and/or OMT to treat CCS or related cardiovascular conditions. No literature related to legal considerations associated with revascularisation and/or OMT was identified.

Regarding ethical issues, the evidence base indicated that treating physicians must ensure their patients have a comprehensive understanding of the risks associated with PCI compared to OMT alone, and be responsible for obtaining a patient's detailed consent and advanced care directive prior to the procedure.

Regarding social issues, the evidence base reported that cultural distrust of healthcare providers, how patients perceive their illness, and assumptions made by healthcare providers based on a patient's social characteristics can all impact the level of care a patient receives. However, these findings are USA-centric and such concerns may not be applicable within the Swiss healthcare context.

The only organisational issue associated with CCS treatment was how social issues (e.g. socioeconomic status, illness perception) directly affect a patient's adherence to OMT (with or without revascularisation). The evidence base indicated that ethical, social and organisational issues can be overcome with patient and physician education and shared decision-making between patients and their treating physicians.

9.1 Methodology: ethical, legal, social and organisational issues

The systematic literature searches detailed in ***Section 7.1.1*** sought literature relevant to legal, social, ethical and organisational issues related to PCI, CABG and/ or OMT in symptomatic patients with CCS or similar cardiovascular disease. Targeted non-systematic keyword searches for literature addressing these domains were also conducted (***Table 60*** in ***Appendix A***). Systematic reviews, literature reviews, RCTs, nonrandomised studies, single-arm studies, ethnographic studies, phenomenological studies, narrative research and case studies were considered for inclusion. The included literature was assembled in tables describing the study characteristics and findings, with the results described narratively.

9.2 Results: ethical, legal, social and organisational issues

9.2.1 Study characteristics

Ten publications were identified via systematic and non-systematic searches for ethical, legal, social and organisational issues.[138,139,141-147] All included publications detailed relevant issues associated with the use of revascularisation and/or OMT for CCS or similar cardiovascular conditions (***Table 55***). Of the publications, 1 reported ethical considerations, 6 detailed social considerations and 4 described organisational considerations reported across Australia (k = 1), Europe (k = 1), the UK (k = 1) and USA (k = 7).[138,139,141-147] None of the identified literature highlighted legal considerations. A PRISMA diagram (***Figure 1***) is reported in ***Section 7.2***.

Table 55 Characteristics of included studies for ethical, legal, social and organisational issues

Study; country	Indication; sample size (n)	Design; duration; setting	Outcomes
Ethical issues			
Blankenship et al. 2013[139] USA	PCI + OMT; OMT Total: NA	Consensus statement American Society for Cardiovascular Angiography and Interventions;	• Patient consent • Advanced care directives
Legal issues			
NA			
Social issues			
Ambrosio et al. 2019[138] Europe	PCI + OMT; CABG + OMT; OMT Total: n = 2,636	Cross-sectional; Multicentre	• Assumptions made by healthcare providers
Fennessy et al. 2013[141] USA	PCI + OMT n = 90; OMT n = 90 Total: n = 180	Prospective cohort; 1 mo; Single-centre	• Illness perception
Gordon et al. 2004[141] USA	PCI + OMT; CABG + OMT Total: n = 681	Prospective cohort; 3 mo; Single-centre	• Assumptions made by healthcare providers
Mitchell et al. 2015[144] USA	Invasive cardiac procedures in CCS	Cross-sectional; Multicentre	• Assumptions made by healthcare providers

Study; country	Indication; sample size (n)	Design; duration; setting	Outcomes
Van Ryn & Burke 2000[146] USA	PCI + OMT; CABG + OMT; OMT Total: n = 618	Cross-sectional; Multicentre	• Assumptions made by healthcare providers
Yuan et al. 2021[147] USA	PCI + OMT; OMT Total: n = 87	Prospective cohort; 6 mo; Multicentre	• Cultural distrust of healthcare providers • Assumptions made by healthcare providers
Organisational issues			
Brewer et al. 2002[140] USA	OMT Total: n = 169	Cross-sectional; Single-centre	• Adherence
Fennessy et al. 2013[141] USA	PCI + OMT; OMT Total: n = 180	Prospective cohort; 1 mo; Single-centre	• Adherence
Horne & Weinman, 1999[143] UK	Medical therapy Total: n = 324	Cross-sectional; Single-centre	• Adherence
Stafford, Jackson & Berk 2008[145] Australia	PCI +OMT; CABG + OMT; OMT Total: n = 229	Prospective cohort; 11 mo; Single-centre	• Adherence

Abbreviations:
CABG: coronary artery bypass; **mo:** month; **n:** sample size; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention.

9.2.2 Findings: ethical issues

A consensus statement published in 2013 by the American Society for Cardiovascular Angiography and Interventions detailed ethical considerations related to revascularisation and OMT.[139] The statement focused on ethical issues concerning the treating physician's responsibility to obtain informed consent and advanced care directives from CCS patients prior to a PCI procedure. Consent must be obtained to ensure that patients, particularly high-risk patients (i.e. those with multivessel disease, disease in critical coronary vessels and/or comorbidities), understand the risks and goals of the PCI procedure. Otherwise, CCS patients may overestimate the benefit and/or success of PCI and underestimate that of OMT alone. It is imperative that treating physicians provide patients with a detailed understating of the benefits of alternative therapy to PCI, such as OMT. Similarly, given the risks associated with PCI, it is important that treating physicians have a detailed understanding of a patient's advanced care directives prior to

the procedure to understand when to terminate treatment during the procedure and when to continue. The consensus statement did not consider ethical issues associated with CABG.

The Society provides 3 recommendations to aid physicians in conveying the risks associated with PCI to their patients and sharing information (i.e. informed consent, advanced care directives) prior to the procedure.[139] It is recommended that physicians provide patients with sufficient time to ask questions and consult with caregivers and family; that physicians enable an exchange of information between themselves and the patient (including relevant family or caregivers); and that physicians employ a patient-specific approach and tailor risks and benefits of PCI to each patient's unique CCS characteristics.

9.2.3 Findings: legal issues

None of the included literature highlighted legal issues related to revascularisation (PCI and/or CABG) and/or OMT in CCS patients.

9.2.4 Findings: social issues

Six studies detailed social issues associated with PCI plus OMT and OMT alone.[141,142,144,146,147] Social issues highlighted in these publications include how patients perceive their illness, cultural distrust of healthcare providers, and how assumptions made by healthcare providers based on social characteristics impact the care that a patient receives.[141,142,144,146,147]

Evidence provided by Fennessy et al. 2013 indicated that how patients perceives their illness—acute or chronic—impacts their adherence to treatment protocols.[141] For example, after 1 month of treatment CCS patients treated with PCI (with concurrent OMT) viewed their illness as acute and thus had lower adherence rates relative to CCS patients allocated to OMT alone.[141] A possible reason for this lower adherence may be that CCS patients mistakenly view PCI as a 'cure' after being discharged from hospital, and subsequently are less vigilant with their prescribed OMT regimen.[141] Patients allocated to the OMT-alone arm of the trial viewed their illness as chronic rather than acute and had greater treatment adherence compared to patients in the PCI trial arm.[141] However, after 1 month of OMT treatment and ongoing CCS symptoms, patients in the OMT arm of the trial demonstrated a reduced belief in the level of symptom control that their prescribed regimen provided.[141]

Cultural distrust of healthcare providers and treating physician bias has a greater influence on CCS patient treatment options than patient or provider knowledge in the USA.[141,142,144,146,147] A single study indicated that cultural distrust of healthcare providers can be caused by a patient's prior experience, religious affiliation or race. Yuan et al. 2021 determined that race was a large predictor of treatment preferences for CCS patients—people of African descent were 4 times more likely to choose OMT over PCI.[147]

Five studies reported physician bias towards CCS patients of African descent, female patients and those of lower socioeconomic status.[138,141,142,144,146] Treating physicians discriminate against these groups by assuming they have lower intelligence, less severe symptoms, lower medication adherence and increased likelihood of risky behaviours.[138,146,147] This physician bias leads to CCS patients of African descent and those of lower socioeconomic status undergoing revascularisation procedures (i.e. PCI or CABG) even when they could benefit from OMT alone.[142,144,147] This increased likelihood of revascularisation remains, even after controlling for confounding effects (i.e. age, race, education).[147] Similarly, Ambrosio et al. 2019 reported that physicians perceived the symptoms of women to be less severe even though they reported higher rates of angina, breathing difficulties, tachycardia and anxiety than their male counterparts.[138]

To overcome these social issues associated with revascularisation and/or OMT alone, there needs to be improvement in the shared decision-making between patients and their treating physicians, as well as comprehensive patient and physician education.[141,142,144,146,147]

9.2.5 Findings: organisational issues

The main organisational issue highlighted in the evidence base (k = 4) was patient adherence to OMT.[140,141,143,145] The included literature indicated that patient perception is the main factor influencing CCS patient adherence. Patients who understood the seriousness of CCS and/or related cardiovascular disease had greater adherence to OMT than those who did not.[140,141,143,145] For example, Brewer et al. found that adherence to OMT was 76% for patients with hypercholesterolaemia who understood the consequences of poor OMT management, while it was only 62% among patients who did not.[140] Similarly, Stafford, Jackson & Berk found increased adherence in patients with coronary heart disease who understood the seriousness of the condition, compared to those who did not.[145] These findings had controls applied for depression, education, disease severity, age, social support and social desirability.[145] Two further studies found that improved patient perception of chronic illness increased adherence to OMT.[141,143]

To overcome issues of perception affecting patient adherence to OMT there must be improvement in patient education around the benefits of medication adherence.[140,141,143,145]

10 Additional issues

10.1 Clinical practice guidelines

Clinical practice guidelines were sought for recommendations on the use of revascularisation (PCI/CABG) and OMT for treatment of CCS in countries with similar levels of economic development to Switzerland. The 2 current guidelines identified—from Europe[37] and USA[186]—are summarised in ***Table 56*** and ***Table 57***. These guidelines are based on composite evidence (RCTs, meta-analyses, large cohort studies, expert opinion), including studies that failed to meet the threshold for inclusion in the current HTA assessment (e.g. data from countries outside the WHO Mortality Stratum A, studies using placebo comparators and studies using PCI bare-metal stents). Definitions for the strength of evidence also differed between the European and American guidelines.

The European and USA guidelines both recommend that patients undergoing coronary angiography should be informed of the benefits and risks associated with the X-ray imaging procedure and likewise informed of the benefits and risks of revascularisation. Non-invasive functional imaging for ischaemia may be an option if there is need to verify the diagnosis. The USA guideline recommends that for patients requiring revascularisation, treatment decisions should be based on clinical indication regardless of sex, race or ethnicity. A shared decision-making approach that includes patients' preferences should be adopted.

Both the European and USA guidelines recommended use of SYNTAX scores to assess complexity of CAD to guide revascularisation decisions. The European guideline recommends SYNTAX scores to determine the long-term risk of mortality and morbidity after PCI.

The European guideline recommends that Society of Thoracic Surgeons scores be calculated to assess hospital mortality and morbidity after CABG. EuroSCORE II may also be considered to assess hospital mortality after CABG to aid with revascularisation choices between CABG and PCI. The USA guideline recommends the use of risk scores from the Society of Thoracic Surgeons to help assess risk of death with CABG.

Criteria used to recommend revascularisation options varied between the European and USA guidelines regarding stratification of subpopulations. The European guidelines recommend myocardial revascularisation for patients with chronic HF and systolic left ventricular dysfunction (ejection fraction ≤35%) suitable for intervention. CABG is recommended as the first revascularisation strategy of choice for patients with multivessel disease and acceptable surgical risk. For patients with 1- or 2-vessel disease, PCI should be considered as an alternative to CABG when complete revascularisation can be

achieved. For patients with 3-vessel disease, PCI should be considered after clinical evaluation and review of diabetes status and presence of comorbidities.

The USA guideline recommends that CABG may be a reasonable option to improve survival compared to OMT for patients with stable ischaemic heart disease (SIHD), normal ejection fraction, significant stenosis in 3 major coronary arteries (with or without proximal LAD) and anatomy suitable for CABG. In patients with SIHD, normal ejection fraction, significant stenosis in 3 major coronary arteries (with or without proximal LAD) and anatomy suitable for PCI, the usefulness of PCI to improve survival is uncertain compared to OMT.

Table 56 Summary of USA clinical practice guidelines and recommendations

Author; country	Recommendation	Strength of recommendation
2021 USA Guideline for Coronary Artery Revascularization[186]		
Recommendation to improve equity of care in revascularisation		
In patients who require coronary revascularisation, treatment decisions should be based on clinical indication regardless of sex, race or ethnicity, and efforts to reduce disparities of care are warranted.		Class 1 Level B-NR
Recommendation for the heart team		
In patients where the optimal treatment strategy is unclear, a Heart Team approach that includes representatives from interventional cardiology, cardiac surgery and clinical cardiology is recommended to improve patient outcomes.		Class 1 Level B-RB
Recommendations for shared decision-making and informed consent		
In patients undergoing revascularisation, decisions should be patient-centred—that is, considerate of the patient's preferences and goals, cultural beliefs, health literacy and social determinants of health—and made in collaboration with the patient's support system.		Class 1 Level C-LD
In patients undergoing coronary angiography or revascularisation, adequate information about benefits, risks, therapeutic consequences and potential alternatives in the performance of percutaneous and surgical myocardial revascularisation should be given, when feasible, with sufficient time for informed decision-making to improve clinical outcomes.		Class 1 Level C-LD
Recommendations for revascularisation to improve survival in CCS compared to medical therapy		
In patients with SIHD and significant left main stenosis, CABG is recommended to improve survival.		Class 1 Level B-NR
In selected patients with SIHD and significant left main stenosis for whom PCI can provide equivalent revascularisation to that possible with CABG, PCI is reasonable to improve survival.		Class 2a Level B-NR
Recommendations for revascularisation to improve survival in CCS compared to medical therapy		
In patients with SIHD, normal ejection fraction, significant stenosis in 3 major coronary arteries (with or without proximal LAD) and anatomy suitable for CABG, CABG may be reasonable to improve survival.		Class 2b Level B-R
In patients with SIHD, normal ejection fraction, significant stenosis in 3 major coronary arteries (with or without proximal LAD) and anatomy suitable for PCI, the usefulness of PCI to improve survival is uncertain.		Class 2b Level B-R
Recommendation for bypass conduits in patients undergoing CABG		
In patients undergoing isolated CABG, the use of a radial artery is recommended in preference to a saphenous vein conduit to graft the second most important, significantly stenosed, non-LAD vessel to improve long-term cardiac outcomes.		Class 1 Level B-R
Recommendations for radial and femoral approaches for PCI		

Author; country	Recommendation	Strength of recommendation
In patients with ACS undergoing PCI, a radial approach is indicated in preference to a femoral approach to reduce the risk of death, vascular complications or bleeding.		Class 1 Level A
In patients with SIHD undergoing PCI, the radial approach is recommended to reduce access site bleeding and vascular complications.		Class 1 Level A
Recommendation for dual antiplatelet therapy in patients after PCI		
In selected patients undergoing PCI, shorter duration DAPT (1 to 3 months) is reasonable with subsequent transition to P2Y12 inhibitor monotherapy to reduce the risk of bleeding events.		Class 2a Level A
Recommendations for revascularisation of the non-infarct artery in patients with STEMI		
In selected hemodynamically stable patients with STEMI and multivessel disease, after successful primary PCI, staged PCI of a significant non-infarct artery stenosis is recommended to reduce the risk of death or MI.		Class 1 Level A
In selected patients with STEMI with complex multivessel non-infarct artery disease, after successful primary PCI, elective CABG is reasonable to reduce the risk of cardiac events.		Class 2.a Level C-EO
In selected hemodynamically stable patients with STEMI and low-complexity multivessel disease, PCI of a non-infarct artery stenosis may be considered at the time of primary PCI to reduce cardiac event rates.		Class 2b Level B-R
In patients with STEMI complicated by cardiogenic shock, routine PCI of a non-infarct artery at the time of primary PCI should not be performed because of the higher risk of death or renal failure.		Class 3 (Harm) Level B-R
Recommendations for patients with diabetes		
In patients with diabetes and multivessel CAD with involvement of the LAD, who are appropriate candidates for CABG, CABG (with a LIMA to the LAD) is recommended in preference to PCI to reduce mortality and repeat revascularisations.		Class 1 Level A
In patients with diabetes, who have multivessel CAD amenable to PCI and an indication for revascularisation and are poor candidates for surgery, PCI can be useful to reduce long-term ischaemic outcomes.		Class 2a Level B-NR
In patients with diabetes, who have left main stenosis and low- or intermediate-complexity CAD in the rest of the coronary anatomy, PCI may be considered an alternative to CABG to reduce major adverse cardiovascular outcome.		Class 2b Level B-R
Recommendation for predicting patient risk of death with CABG		
In patients who are being considered for CABG, calculation of the Society of Thoracic Surgeons risk score is recommended to help stratify patient risk.		Class 1 Level B-NR
Recommendation for defining coronary artery lesion complexity: calculation of the SYNTAX score		
In patients with multivessel CAD, an assessment of CAD complexity such as the SYNTAX score may be useful to guide revascularisation.		Class 2b Level B-NR

Abbreviations

CABG: coronary artery bypass graft; **CAD**: coronary artery disease; **LAD**: left anterior descending artery; **LIMA**: left internal mammary artery; **PCI**: percutaneous coronary intervention; **STEMI**: ST-Elevation Myocardial Infarction; **STS**: Society of Thoracic Surgeons.

Notes

Class (Strength of recommendation) Class 1 = strong; Class 2a = moderate; Class 2b = weak; Class 3 = no benefit (moderate); Class 3 = harm (strong)

Level (quality) of evidence

Level A = high quality evidence

Level B-R = randomised, moderate quality from 1 or more RCT; meta-analyses of moderate quality RCTs

Level B-NR = moderate quality evidence from 1 or more well-designed, well-executed NRSI, observational study or registry study and meta-analyses of such studies (nonrandomised)

Level C-LD = limited data; randomised or nonrandomised observational or registry studies with limitation of design or execution.

Level C-EO = expert opinion; consensus based on clinical experience

Table 57 Summary of European clinical practice guidelines and recommendations

Author; country	Recommendation	Strength of recommendation
European guidelines on myocardial revascularisation (ESC) (EACTS)[37]		
Recommendations for decision-making and patient information in the elective setting		
It is recommended that patients undergoing coronary angiography are informed about benefits and risks, as well as potential therapeutic consequences, ahead of the procedure.		Class I Level C
It is recommended that patients are adequately informed about short- and long-term benefits and risks of the revascularisation procedure with information about local experience, and allowed enough time for informed decision-making.		Class I Level C
It is recommended that institutional protocols are developed by the Heart Team to implement the appropriate revascularisation strategy in accordance with current guidelines.		Class I Level C
In PCI centres without on-site surgery, it is recommended that institutional protocols are established with partner institutions providing cardiac surgery		Class I Level C
Recommendations on criteria for the choice between CABG and PCI		
Assessment of surgical risk		
It is recommended that the STS score is calculated to assess in-hospital or 30-day mortality, and in-hospital morbidity after CABG		Class I Level B
Calculation of the EuroSCORE II score may be considered to assess in-hospital mortality after CABG.		Class IIb Level B
Assessment of CAD complexity		
In patients with LM or multivessel disease, it is recommended that the SYNTAX score is calculated to assess the anatomical complexity of CAD and the long-term risk of mortality and morbidity after PCI.		Class I Level B
When considering the decision between CABG and PCI, completeness of revascularisation should be prioritised.		Class IIa Level B
Recommendations on revascularisations in patients with chronic heart failure and systolic left ventricular dysfunction (ejection fraction ≤35%)		
In patients with severe LV systolic dysfunction and coronary artery disease suitable for intervention, myocardial revascularisation is recommended.		Class I Level B
CABG is recommended as the first revascularisation strategy choice in patients with multivessel disease and acceptable surgical risk.		Class I Level B
In patients with 1- or 2-vessel disease, PCI should be considered as an alternative to CABG when complete revascularisation can be achieved.		Class IIa Level C
In patients with 3-vessel disease, PCI should be considered based on the evaluation by the Heart Team of the patient's coronary anatomy, the expected completeness of revascularisation, diabetes status and comorbidities.		Class IIa Level C
LV aneurysmectomy during CABG should be considered in patients with NYHA class III/IV, large LV aneurysm, large thrombus formation or if the aneurysm is the origin of arrhythmias.		Class IIa Level C
Surgical ventricular restoration during CABG may be considered in selected patients treated in centres with expertise.		Class IIb Level B

Abbreviations:

CABG: coronary artery bypass graft; ; **CAD**: coronary artery disease; **LAD**: left anterior descending artery; **LIMA**: left internal mammary artery; **LM**: left main; **LV**: left ventricular; **PCI**: percutaneous coronary intervention; **NYHA**: New York Heart Association; **SIHD**: stable ischaemic heart disease; **STEMI**: ST-Elevation Myocardial Infarction; **STS**: Society of Thoracic Surgeons.

Class of recommendations

Class I = evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
Class II = conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure
Class IIa = weight of evidence/opinion is in favour of usefulness/efficiency
Class IIB = usefulness/efficacy is well established by evidence/opinion
Class III = evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Levels of evidence:

A = data derived from multiple RCTs or meta-analyses
B = data derived from a single RCT or large nonrandomised studies
C= consensus of opinion of experts and/or small studies, retrospective studies, registries

10.2 Ongoing clinical trials

Ongoing clinical trials (k = 2) meeting the PICO criteria are summarised in ***Table 94*** (***Appendix E***). One RCT (NCT03563417) estimates recruiting 1,560 participants with CTO and randomising participants to PCI or OMT. Participants are recruited from European countries primarily from WHO stratum A. PCI revascularisation will be conducted with the latest generation drug eluting stents (DES) to test the hypothesis that they are superior to OMT in terms of relative reduction in major adverse cardiovascular and cerebrovascular events. Participants will be followed-up for 5 years. The trial started in November 2018 and will finish in November 2023. The second RCT (NCT03756870), estimates recruiting 82 participants with CTO. Participants will be randomised to PCI plus OMT or OMT alone. Participants will be recruited from the Netherlands and followed-up for 10 years. The trial started in July 2019 and will finish in January 2029. Outcome measures will include the Seattle Angina Questionnaire and HRQoL using the Minnesota Living with Heart Failure Questionnaire.

11 Discussion

11.1 Comparison with existing SRs and HTA reports

11.1.1 Comparison with existing effectiveness and safety literature

Direct comparison to published literature is constrained due to different inclusion criteria (e.g. literature reviews not restricting participants to WHO Mortality Stratum A countries, different outcome measures used, outcomes measured and collated at different timepoints, studies using only bare-metal stents [BMS], or participants with greater morbidity included).

In a network meta-analysis of RCTs comparing OMT with CABG in patients with CCS, Windecker et al. found that CABG reduced all-cause mortality compared with OMT.[150] The analysis for this HTA found no significant difference in all-cause mortality at 5-year follow-up, but at 10-year follow-up the analysis was consistent with the network meta-analysis outcome that participants receiving CABG had lower mortality. The network meta-analysis also found that new generation DES, but not early generation DES or BMS, were associated with improved survival compared with initial OMT. The analyses for this HTA could not confirm this because the included trials used multigenerational stents. The network meta-analysis corresponded to the results of this HTA, finding that CABG reduces the risk of MI compared with initial OMT and reduces the risk of subsequent revascularisation.

A meta-analysis of 6 RCTs comparing PCI plus OMT with OMT in CCS patients was congruous with the analysis of this HTA that there were no significant differences between PCI plus OMT and OMT alone for all-cause mortality or MI.[187] A meta-analysis by Laukkanenen et al. of 11 RCTs also found no significant difference for all-cause mortality between PCI plus OMT and OMT alone.[188] Shah and Hajouli reported similar findings that PCI plus OMT was not associated with lower all-cause mortality or MI compared to OMT alone.[189] However, PCI plus OMT was associated with a lower risk for subsequent revascularisation compared to OMT alone, congruent with the results of this HTA up to 24 months follow-up. The results of the current HTA align with the findings of reviews attempting to answer similar safety and effectiveness questions, albeit with more heterogeneous inclusion criteria compared to this HTA.

11.1.2 Comparison with existing economic literature

11.1.2.1 CABG plus OMT vs OMT

The only identified cost-effectiveness study on CABG plus OMT was specific to patients with CCS and LVEF ≤35% (***Section 8.2.2.1***). The study reported that CABG had 25%, 87% and 97% probability of being cost effective at WTP thresholds of US$50,000, US$100,000 and US$150,000, respectively, in these selected high-risk patients.[128] When the mortality benefit was assumed to attenuate beyond 10

years (as assumed in the analysis for this HTA), these probabilities reduced to 7%, 63% and 89%, respectively. In the model for this HTA, when considering baseline event rates specific to patients with CCS and LVEF ≤35%, CABG had 5%, 55% and 85% probability of being cost effective at WTP thresholds of CHF50,000, CHF100,000 and CHF150,000, respectively (***Appendix F***, ***Figure 69***).

11.1.2.2 PCI plus OMT vs OMT

Three identified cost-effectiveness studies on PCI plus OMT used data from the FAME 2 RCT (1 model-based, 2 trial-based; ***Section 8.2.2.2***). The model-based evaluation reported that FFR-guided PCI could be cost effective in patients with angina, with PCI plus OMT demonstrating a 50.4% probability of being cost effective over OMT at the implicit WTP threshold of ¥5 million.[134] Notably, when HRQoL improvements with PCI were limited to a period of 2 years only, the ICER was well above the implicit WTP threshold. PCI was modelled as being associated with lower rates of subsequent revascularisation and MI and a higher rate of stroke relative to OMT; however, mortality rates were equivalent across arms.[134] The cost-effectiveness of PCI plus OMT became more favourable in scenario analyses for this HTA, which assumed no difference in mortality rates and adjusted the time period over which HRQoL benefits were assumed to persist (***Section 8.3.4.2.5***). When mortality rates were applied equally across arms, the ICER inverted from PCI being dominated to a benefit of CHF336,396. When, in addition to this, the HRQoL benefit was extrapolated to persist for 2- or 5-year periods, the ICER reduced further to CHF174,395 and CHF75,522, respectively. Results of these scenario analyses suggest that cost-effectiveness outcomes for the PCI plus OMT vs OMT comparison are largely impacted by the relative effect of PCI plus OMT with respect to all-cause mortality. There is no evidence of a differential effect. Moreover, uncertainty in the extrapolation of HRQoL benefit beyond 12 months after PCI appears to be a driver of cost-effectiveness.

Other model-based evaluations have found PCI to be a cost-effective intervention for patients with CCS who are candidates for PCI (i.e. patients with CCS and angiographic confirmation of significant stenosis), as well as CCS patients with CTO. This HTA did not specifically assess the cost-effectiveness of PCI for CTO. Data from the Swiss PCI survey show that interventions for CTO accounted for 5.3% to 6.4% of PCIs in Switzerland (2018–2020 data).[33,149,184] In the FAME 2 study, 3.4% of lesions were totally occluded.[108]

An economic evaluation performed as part of a German HTA concluded that PCI could not be considered cost-effective in patients with stable angina (***Section 8.2.2.2***).[131,132,137] The German HTA reported the ICER as added cost per patient year free from angina, making comparison difficult.[132]

11.2 Limitations in the clinical analysis

The results of this HTA report should be considered with an understanding of the limitations of the chosen methodology and limitations of the available data.

*11.2.1 **RCT** findings*

The RCT evidence for revascularisation (PCI or CABG) and OMT did not indicate clinical benefits against OMT alone on several outcomes (i.e. MACE, all-cause mortality, hospitalisation, stroke or MI). In the ISCHEMIA and BARI 2D trials the majority of patients underwent revascularisation with PCI rather than CABG. [12,106,112-114] This pooling of 2 types of revascularisation may have influenced the results by diminishing the treatment effect of CABG.

*11.2.2 **NRSI** findings*

NRSIs were included in this HTA to provide additional evidence of intervention effects from cohort studies with participants with CCS in clinical settings. Prognostic risk factors are likely to be unbalanced in the absence of randomisation, leading to confounding variables that could have influenced clinical outcomes. Only NRSIs that used statistical methods to correct for such imbalances (e.g. propensity score matching) were included.

The results from NRSIs can sometimes differ from results from randomised studies and can produce misleading results, even when treatment and control groups appear similar in prognostic factors, because residual confounding factors may still be high. NRSIs are at greater risk of selection bias whereby participant characteristics differ, and choice of intervention is largely determined by the clinician's personal preference or patient preference.[190] This may result in incomparable treatment groups due to one arm being more severely ill. In addition, unaccounted study drop-outs could have introduced attrition bias. The extent of this is unreported, thus the subsequent potential bias is unknown. These factors make the NRSIs more difficult to interpret. As such, the RCT evidence was deemed to provide more reliable results and was used as the basis for the economic evaluation. Assessment of publication bias was not possible due to limited data (<10 trials) that precluded statistical tests. Therefore, it is unknown if the current evidence is biased due to selective publication of positive trials. Typically, negative studies are more likely to remain unpublished than positive studies, leading to overestimation of treatment effects.[191]

11.2.3 Assessment of heterogeneity

Heterogeneity was observed in some of the meta-analyses. However, due to the limited amount of evidence (<10 trials) included in each meta-analysis (RCT or NRSI), it was not possible to conduct subgroup and/or meta regression analyses to assess the impact of individual patient characteristics (i.e. comorbidities, sex, refractory angina, LCMA stenosis >50%, LVEF <40%) or prior revascularisation on the effectiveness and safety of CABG plus OMT or PCI plus OMT compared to OMT alone. Therefore, the causation of the heterogeneity is unknown. Trials used 'intention to treat' analysis in preference to 'as treated' analysis. Both methods have advantages and limitations. Intention-to-treat does not have a consistent definition and is often used inconsistently in study reports, which could be a source of heterogeneity, and treatment cross-over during patient follow-up is a potential confounding variable.[192]

11.3 Limitations in the economic analysis

All economic models are a simplification of reality. Complex patient experiences are condensed and reflected as transitions through a limited number of health states. One limitation of the model used in this evaluation was that it did not track patient history of non-fatal MACE events. Therefore, the impact on future event risks and long-term (>1 year) costs could not be captured. As such, the full benefit of avoided MACE events may not be captured. This could bias against interventions that significantly reduce the risk of such events. Furthermore, apart from all-cause mortality, which was linked to age, risks of all other MACE events were assumed to remain constant over time, regardless of patient age or duration of CCS.

An important challenge lay in defining the target population and the most appropriate baseline event risks for each comparison. There were uncertainties in defining the general Swiss CCS cohort and the Swiss CCS cohorts who would be considered for revascularisation. Individual RCTs were the preferred source of baseline transition probabilities, given differences in eligibility criteria across studies. Nevertheless, uncertainties remain regarding how accurately the baseline event rates reflect target populations within the Swiss context.

The economic evidence hinted at potential differences in cost-effectiveness according to patient characteristics and comorbidities. However, only limited subgroup analyses were undertaken, informed by the targeted population groups considered in previous RCTs. Given the complexities in treatment decision-making for CCS, this is an area for further research.

Limitations are present in the approach taken to model transitions within the intervention arm. Over trial follow-up, transition probabilities were derived by multiplying baseline annual event rates by estimates of risk ratio. A limitation exists in that the relative effect of treatment was assumed to be constant over the follow-up period. Beyond trial follow-up, transition probabilities were derived from baseline annual

event rates. It was assumed that any benefits of treatment would attenuate beyond the last observation point. This was a modelling assumption, albeit conservative. It should be noted that other extrapolation approaches could have been adopted.

11.4 Evidence gaps

Trials evaluating PCI interventions used multigeneration stents because the study enrolment period overlapped with advances in new stent technology. None of the trials included participants revascularised exclusively with third generation DES. Therefore, an evidence gap exists regarding the safety and efficacy of third generation DES compared to OMT.

12 Conclusions

12.1 Clinical evaluation

Overall, the evidence-base presented varying results across the different interventions (CABG, PCI or revascularisation [CABG or PCI]) and study designs (RCT or NRSI). Intervention-specific results are detailed below (***Sections 12.1.1, 12.1.2 and 12.1.3***).

Differences between RCT and NRSI results for the same intervention cannot be explained easily. The RCT study design provides a higher quality of evidence and is not subject to the residual confounding factors that affect adjusted NRSIs; therefore, the conclusions are based on the RCT results.

12.1.1 CABG plus OMT vs OMT alone

The RCT evidence reported generally favourable outcomes for the use of CABG plus OMT compared to OMT alone. The evidence reported favourable long-term outcomes for MACE (60–120 months), all-cause mortality (120 months), hospitalisation (including due to HF; 60–120 months) and MI (120 months). Similarly, there was a favourable short-term (≤ 24 months) outcome reported for HRQoL (general and cardiac-specific). The RCT evidence reported no significant difference in stroke rates for the use of CABG plus OMT compared to OMT alone. Additionally, none of the included RCTs reported data for TVR. The treatment effect ranged from small to large, and the evidence base was rated as having a moderate risk of bias.

12.1.2 PCI plus OMT vs OMT alone

The RCT evidence reported mixed results for PCI plus OMT compared to OMT alone. Short-term results favouring PCI plus OMT were reported for HRQoL (general HRQoL [12 months], cardiac-specific HRQoL [12 months], angina frequency [12 months]) and subsequent revascularisation (12-24 months). MACE scores at 12 and 60 months were not significantly different compared to OMT alone, but 24-month results from a single study significantly favoured PCI plus OMT. The RCT evidence reported long-term (≥60 months) outcomes for MI favouring PCI plus OMT compared to OMT (no difference at 12-24 months). No significant differences were reported at any time point for all-cause mortality, hospitalisation, stent thrombosis or stroke. Furthermore, none of the included RCTs reported data for TVR or hospitalisation due to HF. The treatment effect ranged from small to large and the evidence base presented a moderate to high risk of bias.

12.1.3 Revascularisation plus OMT vs OMT alone

The RCT evidence on revascularisation plus OMT reported limited overall benefit in relation to the important outcomes measured for this HTA. Outcomes favouring revascularisation plus OMT included subsequent revascularisation (60 months), angina frequency (12 months) cardiac-specific HRQoL (12 months), and treatment satisfaction (12-24 months). Regarding hospitalisation due to HF, the RCT evidence demonstrated unfavourable long-term outcomes (60 months) for revascularisation plus OMT. Importantly, the RCT evidence reported no significant differences in MACE, all-cause mortality, hospitalisation, MI or stroke. Moreover, none of the included RCTs reported data for TVR, stent thrombosis or general HRQoL. The treatment effect ranged from small to large and the evidence base presented a moderate to high risk of bias. The efficacy of revascularisation may have been affected by the higher proportion of PCI patients (compared to CABG patients) in the RCT (ISCHEMIA and BARI 2D) cohorts.[12,106,112-114]

12.2 Economic evaluation

Economic evaluations using baseline event rates (i.e. event rates for OMT alone) from the ISCHEMIA RCT demonstrated low probabilities that CABG plus OMT, PCI plus OMT and revascularisation plus OMT are cost-effective relative to OMT alone. However, cost-effectiveness of CABG plus OMT and revascularisation plus OMT improved when sourcing baseline event rates from cohorts with higher event risks (i.e. patients with CCS and LVEF<35%; patients with CCS and CKD), suggesting these interventions may be more cost-effective in higher-risk patients. A lack of clinical data on the relative effect of PCI plus OMT vs OMT alone on HRQoL beyond 12 months is a key uncertainty, and base case results should be interpreted cautiously. Given the complexities in treatment decision-making for CCS, cost-effectiveness analysis stratified by patient subgroups is an area for further research.

Under current policy conditions, CABG and PCI procedures for management of CCS were estimated to be responsible for anticipated costs of CHF59.7 million and CHF146.1 million, respectively, in 2023. Considering observed trends in the use of revascularisation procedures over the period 2016 to 2019 (i.e. reducing utilisation of CABG, increasing utilisation of inpatient and outpatient PCI), anticipated CABG costs were projected to decrease to CHF51.2 million in 2027, while anticipated PCI costs were projected to increase to CHF184.3 million. Scenario analyses using alternative data sources and/or assumptions for PCI procedure numbers reported costs for PCI of CHF135.9 million to CHF142.3 million in 2023, and CHF114.1 million to CHF156.2 million in 2027.

13 References

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41(3):407-77.

2. Braun MM, Stevens WA, Barstow CH. Stable Coronary Artery Disease: Treatment. *Am Fam Physician* 2018;97(6):376-84.

3. Smith SC, Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol* 2011;58(23):2432-46.

4. Bernhard M. Forty years of percutaneous coronary intervention. *Cardiovascular Medicine* 2018(11)

5. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39(2):119-77.

6. Chacko L, J PH, Rajkumar C, et al. Effects of Percutaneous Coronary Intervention on Death and Myocardial Infarction Stratified by Stable and Unstable Coronary Artery Disease: A Meta-Analysis of Randomized Controlled Trials. *Circ Cardiovasc Qual Outcomes* 2020;13(2):e006363.

7. Simoons ML, Windecker S. Controversies in cardiovascular medicine: Chronic stable coronary artery disease: drugs vs. revascularization. *Eur Heart J* 2010;31(5):530-41.

8. Pfisterer M, Trial of Invasive versus Medical therapy in Elderly patients I. Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME). *Circulation* 2004;110(10):1213-8.

9. Pfisterer M, Buser P, Osswald S, et al. Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: one-year results of the randomized TIME trial. *JAMA* 2003;289(9):1117-23.

10. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356(15):1503-16.

11. Hueb W, Lopes N, Gersh BJ, et al. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation* 2010;122(10):949-57.

12. Maron DJ, Hochman JS, Reynolds HR, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *N Engl J Med* 2020;382(15):1395-407.

13. Boden WE, Stone PH. To stent or not to stent? Treating angina after ISCHEMIA-why a conservative approach with optimal medical therapy is the preferred initial management strategy for chronic coronary syndromes: insights from the ISCHEMIA trial. *Eur Heart J* 2021;42(14):1394-400.

14. Cleveland Clinic Staff. Coronary Artery Disease Cleveland: Cleveland Clinic; 2021 [updated 21 June 2021. Available from: https://my.clevelandclinic.org/health/diseases/16898-coronary-artery-disease accessed 12 January 2022].

15. Ford TJ, Corcoran D, Berry C. Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. *Heart* 2018;104(4):284-92.

16. Zakkar M, George SJ, Ascione R. Should chronic total occlusion be treated with coronary artery bypass grafting? . *Circulation* 2016;133(18):1807-16.

17. Mayo Clinic Staff. Coronary artery disease Rochester: Mayo Foundation for Medical Education and Research; 2020 [updated 05 June 2020 Available from: https://www.mayoclinic.org/diseases-conditions/coronary-artery-disease/symptoms-causes/syc-20350613 accessed 11 January 2022].

18. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;352(16):1685-95.

19. Boudoulas KD, Triposciadis F, Geleris P, et al. Coronary Atherosclerosis: Pathophysiologic Basis for Diagnosis and Management. *Prog Cardiovasc Dis* 2016;58(6):676-92.

20. Koshy AN, Dinh DT, Fulcher J, et al. Long-term mortality in asymptomatic patients with stable ischemic heart disease undergoing percutaneous coronary intervention. *Am Heart J* 2022;244:77-85.

21. Cassar A, Holmes DR, Jr., Rihal CS, et al. Chronic coronary artery disease: diagnosis and management. *Mayo Clin Proc* 2009;84(12):1130-46.

22. Yeghiazarians Y, Braunstein JB, Askari A, et al. Unstable angina pectoris. *N Engl J Med* 2000;342(2):101-14.

23. Pfisterer ME, Zellweger MJ, Gersh BJ. Management of stable coronary artery disease. *Lancet* 2010;375(9716):763-72.

24. Mayo Clinic Staff. Chest X-rays: Mayo Foundation for Medical Education and Research (MFMER); 2022 [cited 2022 March 17]. Available from: https://www.mayoclinic.org/tests-procedures/chest-x-rays/about/pac-20393494].

25. Mayo Clinic Staff. CT coronary angiogram: Mayo Foundation for Medical Education and Research (MFMER); 2022 [Available from: https://www.mayoclinic.org/tests-procedures/ct-coronary-angiogram/about/pac-20385117 accessed March 17 2022].

26. Feldman DI, Latina J, Lovell J, et al. Coronary computed tomography angiography in patients with stable coronary artery disease. *Trends Cardiovasc Med* 2022;32(7):421-28.

27. John Hopkins Medicine. Positron Emission Tomography (PET): Johns Hopkins University; 2023 [Available from: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/positron-emission-tomography-pet accessed Jan 6 2023].

28. John Hopkins Medicine. Myocardial Perfusion Scan, Stress: Johns Hopkins University; 2023 [Available from: https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/myocardial-perfusion-scan-stress accessed Jan 6 2023].

29. Federal Statistics Office (FSO). Death and its main causes in Switzerland 2018 Online: Federal Statistical Office; 2021 [Available from: https://www.bfs.admin.ch/bfs/en/home/statistics/health/state-health/mortality-causes-death/specific.assetdetail.16644533.html accessed 26 November 2021 2021].

30. World Health Organization (WHO). The top 10 causes of death 2020 [Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death accessed 26 November 2021 2021].

31. Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. *Annu Rev Public Health* 2005;26:469-500.

32. Wilkins E, Wilson L, Wickramasinghe K, et al. European cardiovascular disease statistics 2017: European Heart Network, 2017.

33. Nestelberger T, Twerenbold R, Cook S, et al. Coronary and structural heart interventions in Switzerland 2018. *Swiss Med Wkly* 2020;150:w20200.

34. Murray CJ, Kulkarni SC, Ezzati M. Understanding the coronary heart disease versus total cardiovascular mortality paradox: a method to enhance the comparability of cardiovascular death statistics in the United States. *Circulation* 2006;113(17):2071-81.

35. Zhang KY, Gai LY, Gai JJ, et al. Four-year clinical outcome in asymptomatic patients undergoing coronary computed tomography angiography. *Chin Med J (Engl)* 2013;126(9):1630-5.

36. Escaned J, Collet C, Ryan N, et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J* 2017;38(42):3124-34.

37. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *European heart journal* 2019;40(2):87-165.

38. Mohamed MO, Shoaib A, Gogas B, et al. Trends of repeat revascularization choice in patients with prior coronary artery bypass surgery. *Catheterization and Cardiovascular Interventions* 2021;98(3):470-80.

39. Bourassa MG, Detre KM, Johnston JM, et al. Effect of prior revascularization on outcome following percutaneous coronary intervention; NHLBI Dynamic Registry. *Eur Heart J* 2002;23(19):1546-55.

40. Byrne RA, Sarafoff N, Kastrati A, et al. Drug-eluting stents in percutaneous coronary intervention: a benefit-risk assessment. *Drug Saf* 2009;32(9):749-70.

41. Canfield J, Totary-Jain H. 40 Years of Percutaneous Coronary Intervention: History and Future Directions. *J Pers Med* 2018;8(4)

42. Iqbal J, Gunn J, Serruys PW. Coronary stents: historical development, current status and future directions. *Br Med Bull* 2013;106:193-211.

43. Waksman R, Pakala R. Drug-eluting balloon: the comeback kid? *Circulation: Cardiovascular Interventions* 2009;2(4):352-58.

44. Kayssi A, Al-Atassi T, Oreopoulos G, et al. Drug-eluting balloon angioplasty versus uncoated balloon angioplasty for peripheral arterial disease of the lower limbs. *Cochrane Database of Systematic Reviews* 2016(8)

45. Seedial SM, Ghosh S, Saunders RS, et al. Local drug delivery to prevent restenosis. *Journal of vascular surgery* 2013;57(5):1403-14.

46. Teirstein PS. Drug-eluting stent restenosis: an uncommon yet pervasive problem: Am Heart Assoc, 2010:5-7.

47. Weisz G, Leon MB, Holmes DR, et al. Five-year follow-up after sirolimus-eluting stent implantation: results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial. *Journal of the American College of Cardiology* 2009;53(17):1488-97.

48. Iantorno M, Lipinski MJ, Garcia-Garcia HM, et al. Meta-Analysis of the Impact of Strut Thickness on Outcomes in Patients With Drug-Eluting Stents in a Coronary Artery. *Am J Cardiol* 2018;122(10):1652-60.

49. Luscher TF, Steffel J, Eberli FR, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation* 2007;115(8):1051-8.

50. Diodato M, Chedrawy EG. Coronary artery bypass graft surgery: the past, present, and future of myocardial revascularisation. *Surg Res Pract* 2014;2014:726158.

51. Frazier AA, Qureshi F, Read KM, et al. Coronary artery bypass grafts: assessment with multidetector CT in the early and late postoperative settings. *Radiographics* 2005;25(4):881-96.

52. Møller CH, Penninga L, Wetterslev J, et al. Off-pump versus on-pump coronary artery bypass grafting for ischaemic heart disease. *Cochrane Database Syst Rev* 2012(3):CD007224.

53. Melly L, Torregrossa G, Lee T, et al. Fifty years of coronary artery bypass grafting. *J Thorac Dis* 2018;10(3):1960-67.

54. Abu-Omar Y, Taggart DP. Coronary artery bypass surgery. *Medicine* 2014;42(9):527-31.

55. Sarkar M, Prabhu V. Basics of cardiopulmonary bypass. *Indian J Anaesth* 2017;61(9):760-67.

56. Connolly MW, Subramanian VA, Patel NU. Multivessel coronary artery bypass grafting without cardiopulmonary bypass. *Operative techniques in thoracic and cardiovascular surgery* 2000;5(3):166-75.

57. Stoney WS. Evolution of cardiopulmonary bypass. *Circulation* 2009;119(21):2844-53.

58. Ennker JC, Ennker IC. Coronary artery surgery: now and in the next decade. *HSR Proc Intensive Care Cardiovasc Anesth* 2012;4(4):217-23.

59. Garg S, Raja SG. Minimally invasive direct coronary artery bypass (MIDCAB) grafting. *AME Medical Journal* 2020;5

60. Shekar PS. Cardiology patient page. On-pump and off-pump coronary artery bypass grafting. *Circulation* 2006;113(4):e51-2.

61. Cremer J, Schoettler J, Thiem A, et al. The MIDCAB approach in its various dimensions. *HSR Proc Intensive Care Cardiovasc Anesth* 2011;3(4):249-53.

62. Oxner A, Elbaz-Greener G, Qui F, et al. Variations in Use of Optimal Medical Therapy in Patients With Nonobstructive Coronary Artery Disease: A Population-Based Study. *J Am Heart Assoc* 2017;6(11):e007526.

63. Iqbal AM, Lopez RA, Hai O. Antiplatelet Medications. StatPearls. Treasure Island (FL): StatPearls Publishing

64. Maeder MT, König T, Bogdanovic S, et al. Quality of vitamin K antagonist oral anticoagulation in 322 patients with atrial fibrillation–real-life data from a survey in Eastern Switzerland. *Swiss Medical Weekly* 2017(39)

65. Schäfer HH, Scheunert U. Costs of current antihypertensive therapy in Switzerland: an economic evaluation of 3,489 patients in primary care. *Swiss Medical Weekly* 2013;143(4344)

66. Opie L. Pharmacological differences between calcium antagonists. *European heart journal* 1997;18(suppl_A):71-79.

67. Frishman WH. Calcium channel blockers: differences between subclasses. *American journal of cardiovascular drugs* 2007;7(1):17-23.

68. Clader JW. The discovery of ezetimibe: a view from outside the receptor. *Journal of medicinal chemistry* 2004;47(1):1-9.

69. Bergeron N, Phan BA, Ding Y, et al. Proprotein convertase subtilisin/kexin type 9 inhibition: a new therapeutic mechanism for reducing cardiovascular disease risk. *Circulation* 2015;132(17):1648-66.

70. Cook S, Stauffer J-C, Hess OM, et al. Current outpatient therapy of stable coronary artery disease in Switzerland. *Cardiovascular risk factors* 2010;283(157):126.

71. McNamara RL, Spatz ES, Kelley TA, et al. Standardized Outcome Measurement for Patients With Coronary Artery Disease: Consensus From the International Consortium for Health Outcomes Measurement (ICHOM). *J Am Heart Assoc* 2015;4(5)

72. Werdan K. Nationale Versorgungsleitlinie (NVL) Chronische KHK. *Cme* 2016;13(11):50-68.

73. Bakhai A, Hill RA, Dundar Y, et al. Percutaneous transluminal coronary angioplasty with stents versus coronary artery bypass grafting for people with stable angina or acute coronary syndromes. *Cochrane Database Syst Rev* 2005;2005(1):CD004588.

74. Poudel I, Tejpal C, Rashid H, et al. Major Adverse Cardiovascular Events: An Inevitable Outcome of ST-elevation myocardial infarction? A Literature Review. *Cureus* 2019;11(7):e5280.

75. Bosco E, Hsueh L, McConeghy KW, et al. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. *BMC Med Res Methodol* 2021;21(1):241.

76. Kip KE, Hollabaugh K, Marroquin OC, et al. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. *J Am Coll Cardiol* 2008;51(7):701-7.

77. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. *Ann Intern Med* 1993;118(8):622-9.

78. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473-83.

79. Gori T, Polimeni A, Indolfi C, et al. Predictors of stent thrombosis and their implications for clinical practice. *Nature Reviews Cardiology* 2019;16(4):243-56.

80. Modi K, Soos MP, Mahajan K. Stent thrombosis. StatPearls [Internet]: StatPearls Publishing 2021.

81. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021): Cochrane; 2021 [Available from: www.training.cochrane.org/handbook].

82. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 2009;6(7):e1000097.

83. Endo A. A historical perspective on the discovery of statins. *Proc Jpn Acad Ser B Phys Biol Sci* 2010;86(5):484-93.

84. Sergeant P. The future of coronary bypass surgery. *Eur J Cardiothorac Surg* 2004;26 Suppl 1:S4-6; discussion S6-7.

85. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;5(1):210.

86. World Health Organization. The world health report: shapping the future. List of member states by WHO region and mortality stratum. Geneva: World Health Organization, 2003:182-84.

87. World Health Organization. List of Member States by WHO Region and Mortality Stratum: World Health Organization 2020 [Available from: https://www.who.int/choice/demography/mortality_strata/en/ accessed February 5 2020].

88. Cohen J. A Coefficient of Agreement for Nominal Scales. *Educational and Psychological Measurement* 1960;20(1):37-46.

89. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. *Biometrics* 1977;33(1):159-74.

90. Rohatgi A. WebPlotDigitizer (version 4.5) Pacifica: Ankit Rohatgi; 2021 [Available from: https://automeris.io/WebPlotDigitizer accessed 6 Jan 2022].

91. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.

92. Sleith C. Notes on Methodology Checklisy 3: Cohort Studies: SIGN, 2012.

93. SIGN. Methodology Checklist 3: Cohort studies: SIGN.

94. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.

95. Schünemann H, Brożek J, Guyatt G, et al. GRADE handbook for grading quality of evidence and strength of recommendations: The GRADE Working Group, 2013.

96. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64(4):383-94.

97. Pollock A, Farmer SE, Brady MC, et al. An algorithm was developed to assign GRADE levels of evidence to comparisons within systematic reviews. *J Clin Epidemiol* 2016;70:106-10.

98. GRADEpro GDT. GRADEpro Guideline Development Tool (Software): McMaster University and Evidence Prime; 2021 [Available from: gradepro.org accessed 6 Jan 2022].

99. Maas CJ, Hox JJ, Lensvelt-Mulders GJ. Longitudinal meta-analysis. *Quality and Quantity* 2004;38(4):381-89.

100. R Core Team. R: A language and environment for statistical computing. Vienna: Foundation for Statistical Computing, 2021.

101. R Studio Team. RStudio: Integrated Development for R. RStudio: Boston, 2021.

102. Schwarzer G. Package 'meta': R projects, 2022.

103. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56(2):455-63.

104. Bangalore S, Maron DJ, O'Brien SM, et al. Management of Coronary Disease in Patients with Advanced Kidney Disease. *N Engl J Med* 2020;382(17):1608-18.

105. Carson P, Wertheimer J, Miller A, et al. The STICH trial (Surgical Treatment for Ischemic Heart Failure): mode-of-death results. *JACC Heart Fail* 2013;1(5):400-8.

106. Dagenais GR, Lu J, Faxon DP, et al. Effects of optimal medical treatment with or without coronary revascularization on angina and subsequent revascularizations in patients with type 2 diabetes mellitus and stable ischemic heart disease. *Circulation* 2011;123(14):1492-500.

107. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014;371(13):1208-17.

108. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367(11):991-1001.

109. Doenst T, Cleland JG, Rouleau JL, et al. Influence of crossover on mortality in a randomized study of revascularization in patients with systolic heart failure and coronary artery disease. *Circ* 2013;6(3):443-50.

110. Hennigan B, Berry C, Collison D, et al. Percutaneous coronary intervention versus medical therapy in patients with angina and grey-zone fractional flow reserve values: a randomised clinical trial. *Heart* 2020;106(10):758-64.

111. Mark DB, Knight JD, Velazquez EJ, et al. Quality-of-life outcomes with coronary artery bypass graft surgery in ischemic left ventricular dysfunction: a randomized trial. *Ann Intern Med* 2014;161(6):392-9.

112. Mark DB, Spertus JA, Bigelow R, et al. Comprehensive quality-of-life outcomes with invasive versus conservative management of chronic coronary disease in ISCHEMIA. *Circulation* 2022;145(17):1294-307.

113. Shah B, Srinivas VS, Lu J, et al. Change in enrollment patterns, patient selection, and clinical outcomes with the availability of drug-eluting stents in the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial. *Am Heart J* 2013;166(3):519-26.

114. The BARI 2D Study Group. A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease. *N Engl J Med* 2009;360(24):2503-15.

115. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011;364(17):1607-16.

116. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. *N Engl J Med* 2016;374(16):1511-20.

117. Werner GS, Martin-Yuste V, Hildick-Smith D, et al. A randomized multicentre trial to compare revascularization with optimal medical therapy for the treatment of chronic total coronary occlusions. *Eur Heart J* 2018;39(26):2484-93.

118. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *N Engl J Med* 2018;379(3):250-59.

119. Anderson LL, Dai D, Miller AL, et al. Percutaneous coronary intervention for older adults who present with syncope and coronary artery disease? Insights from the National Cardiovascular Data Registry. *Am Heart J* 2016;176:1-9.

120. Castleberry AW, Williams JB, Daneshmand MA, et al. Surgical revascularization is associated with maximal survival in patients with ischemic mitral regurgitation: a 20-year experience. *Circulation* 2014;129(24):2547-56.

121. Danson EJF, Sapontis J, Kaura A, et al. Long-term outcomes in surgically ineligible patients managed with percutaneous coronary revascularization or medical therapy. *Cardiovasc Interv Ther* 2019;34(3):249-59.

122. Hannan EL, Samadashvili Z, Cozzens K, et al. Comparative outcomes for patients who do and do not undergo percutaneous coronary intervention for stable coronary artery disease in New York. *Circulation* 2012;125(15):1870-9.

123. Ladwiniec A, Allgar V, Thackray S, et al. Medical therapy, percutaneous coronary intervention and prognosis in patients with chronic total occlusions. *Heart* 2015;101(23):1907-14.

124. Phan DQ, Zadegan R, Lee MS. Revascularization versus medical therapy in patients aged 80 and older with stable ischemic heart disease. *J Am Geriatr Soc* 2021;69(12):3457-67.

125. Prestipino F, Spadaccio C, Nenna A, et al. Off-pump coronary artery bypass grafting versus optimal medical therapy alone: effectiveness of incomplete revascularization in high risk patients. *J Geriatr Cardiol* 2016;13(1):23-30.

126. Wijeysundera HC, Bennell MC, Qiu F, et al. Comparative-effectiveness of revascularization versus routine medical therapy for stable ischemic heart disease: a population-based study. *J Gen Intern Med* 2014;29(7):1031-9.

127. Caruba T, Chevreul K, Zarca K, et al. Annual cost of stable coronary artery disease in France: A modeling study. *Arch Cardiovasc Dis* 2015;108(11):576-88.

128. Chew DS, Cowper PA, Al-Khalidi H, et al. Cost-Effectiveness of Coronary Artery Bypass Surgery Versus Medicine in Ischemic Cardiomyopathy: The STICH Randomized Clinical Trial. *Circulation* 2022;145(11):819-28.

129. Fearon WF, Nishi T, De Bruyne B, et al. Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease: Three-Year Follow-Up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). *Circulation* 2018;137(5):480-87.

130. Fearon WF, Shilane D, Pijls NH, et al. Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. *Circulation* 2013;128(12):1335-40.

131. Gada H, Whitlow PL, Marwick TH. Establishing the cost-effectiveness of percutaneous coronary intervention for chronic total occlusion in stable angina: a decision-analytic model. *Heart* 2012;98(24):1790-7.

132. Gorenoi V, Schonermark MP, Hagen A. Percutaneous coronary intervention with optimal medical therapy vs. optimal medical therapy alone for patients with stable angina pectoris. *GMS Health Technol Assess* 2011;7:Doc07.

133. Kang JS, Bennell MC, Qiu F, et al. Relation between initial treatment strategy in stable coronary artery disease and 1-year costs in Ontario: a population-based cohort study. *CMAJ Open* 2016;4(3):E409-E16.

134. Kodera S, Morita H, Kiyosue A, et al. Cost-Effectiveness of Percutaneous Coronary Intervention Compared With Medical Therapy for Ischemic Heart Disease in Japan. *Circ J* 2019;83(7):1498-505.

135. McCreanor V, Parsonage WA, Whiteman DC, et al. Pharmaceutical use and costs in patients with coronary artery disease, using Australian observational data. *BMJ Open* 2019;9(11):e029360.

136. Stenvall H, Tierala I, Rasanen P, et al. Long-term clinical outcomes, health-related quality of life, and costs in different treatment modalities of stable coronary artery disease. *Eur Heart J Qual Care Clin Outcomes* 2017;3(1):74-82.

137. Wijeysundera HC, Tomlinson G, Ko DT, et al. Medical therapy v. PCI in stable coronary artery disease: a cost-effectiveness analysis. *Med Decis Making* 2013;33(7):891-905.

138. Ambrosio G, Collins P, Dechend R, et al. staBle angina: peRceptIon of neeDs, quality of life and manaGemEnt of patients (BRIDGE Study)- a multinational european physician survey. *Angiology* 2019;70(5):397-406.

139. Blankenship JC, Gigliotti OS, Feldman DN, et al. Ad hoc percutaneous coronary intervention: a consensus statement from the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2013;81(5):748-58.

140. Brewer NT, Chapman GB, Brownlee S, et al. Cholesterol control, medication adherence and illness cognition. *British Journal of Health Psychology* 2002;7(4):433-47.

141. Fennessy MM, Devon HA, Ryan C, et al. Changing illness perceptions and adherence to dual antiplatelet therapy in patients with stable coronary disease. *J Cardiovasc Nurs* 2013;28(6):573-83.

142. Gordon HS, Paterniti DA, Wray NP. Race and patient refusal of invasive cardiac procedures. *Journal of General Internal Medicine* 2004;19(9):962-66.

143. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* 1999;47(6):555-67.

144. Mitchell SE, Paasche-Orlow MK, Orner MB, et al. Patient Decision Control and the Use of Cardiac Catheterization. *Global Advances in Health and Medicine* 2015;4(4):24-31.

145. Stafford L, Jackson HJ, Berk M. Illness beliefs about heart disease and adherence to secondary prevention regimens. *Psychosom Med* 2008;70(8):942-8.

146. van Ryn M, Burke J. The effect of patient race and socio-economic status on physicians' perceptions of patients. *Soc Sci Med* 2000;50(6):813-28.

147. Yuan N, Boscardin C, Lisha NE, et al. Is Better Patient Knowledge Associated with Different Treatment Preferences? A Survey of Patients with Stable Coronary Artery Disease. *Patient Prefer Adherence* 2021;15(pp 119-126):119-26.

148. Gaba P, Serruys PW, Karmpaliotis D, et al. Outpatient Versus Inpatient Percutaneous Coronary Intervention in Patients With Left Main Disease (from the EXCEL Trial). *Am J Cardiol* 2021;143:21-28.

149. Wagener M, Twerenbold R, Cook S, et al. Coronary and structural heart interventions in Switzerland 2019. *Swiss Med Wkly* 2021;151:w20495.

150. Windecker S, Stortecky S, Stefanini GG, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. *BMJ* 2014;348:g3859.

151. Komajda M, Cosentino F, Ferrari R, et al. Profile and treatment of chronic coronary syndromes in European Society of Cardiology member countries: The ESC EORP CICD-LT registry. *Eur J Prev Cardiol* 2021;28(4):432-45.

152. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual 2022 [cited 2022 29 July]. Available from: https://www.nice.org.uk/process/pmg20/resources accessed 29 July 2022].

153. *TreeAge Software, version R2.0* [program]. *Williamstown, MA; sofware available at https://www.treeage.com/*, 2022.

154. Drummond MF, Sculpher MJ, Claxton K, et al. Methods for the Economic Evaluation of Health Care Programmes. Fourth Edition. Great Clarendon Street, Oxford, United Kingdom: Oxford University Press 2015.

155. Sorbets E, Fox KM, Elbez Y, et al. Long-term outcomes of chronic coronary syndrome worldwide: insights from the international CLARIFY registry. *Eur Heart J* 2020;41(3):347-56.

156. Bundesamt für Statistik (BFS). Medizinische Statistik der Krankenhäuser (MedStat). Data procured by the Federal Office of Public Health (FOPH), 2022.

157. Bundesinstitut für Arzneimittel und Medizinprodukte. ICD-10-GM Version 2022 2022 [cited 2022 27 October]. Available from: https://www.dimdi.de/static/de/klassifikationen/icd/icd-10-gm/kode-suche/htmlgm2022/index.htm accessed 27 October 2022].

158. Swiss Federal Statistics Office. Swiss Classification of Operations (CHOP). Systematic Index - Version 2022 2022 [cited 2022 27 October]. Available from: https://www.bfs.admin.ch/bfs/de/home/aktuell/neue-veroeffentlichungen.assetdetail.18304268.html accessed 27 October 2022].

159. Groeneveld PW, Suh JJ, Matta MA. The costs and quality-of-life outcomes of drug-eluting coronary stents: a systematic review. *J Interv Cardiol* 2007;20(1):1-9.

160. NewIndex AG. Kantonale Taxpunktwerte 2022 [cited 2022 20 November]. Available from: https://www.newindex.ch/servicebereich/ accessed 20 November 2022].

161. PwC. Ambulant vor stationär – Oder wie sich eine Milliarde Franken jährlich einsparen lassen 2016 [cited 2022 11 November]. Available from: https://www.pwc.ch/de/insights/gesundheitswesen/ambulant-vor-stationar-oder-wie-sich-eine-milliarde-franken-jahrlich-einsparen-lassen.html].

162. SwissDRG. SwissDRG System 11.0/2022 2022 [cited 2022 8 November]. Available from: https://www.swissdrg.org/de/akutsomatik/swissdrg-system-1102022].

163. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2022 2022 [cited 2022 26 October]. Available from: https://www.whocc.no/atc_ddd_index/ accessed 26 October 2022].

164. Bundesamt für Gesundheit BAG. Spezialitätenliste (SL) und Geburtsgebrechen-Spezialitätenliste (GGSL) 2022 [cited 2022 26 October]. Available from: https://www.xn--spezialittenliste-ygb.ch/ accessed 26 October 2022].

165. Twerenbold S, Schur N, Zappalà T, et al. Helsana-Arzneimittelreport für die Schweiz 2021. 2021 [Available from: https://reports.helsana.ch/en/drugs2021/].

166. Lang IM, Badr-Eslam R, Greenlaw N, et al. Management and clinical outcome of stable coronary artery disease in Austria : Results from 5 years of the CLARIFY registry. *Wien Klin Wochenschr* 2017;129(23-24):879-92.

167. Refdata Foundation. Medicinal Product Information [cited 2022 9 August]. Available from: https://www.swissmedicinfo.ch/ accessed 9 August 2022].

168. Maron DJ, Hochman JS, O'Brien SM, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: Rationale and design. *Am Heart J* 2018;201:124-35.

169. Sorbets E, Greenlaw N, Ferrari R, et al. Rationale, design, and baseline characteristics of the CLARIFY registry of outpatients with stable coronary artery disease. *Clin Cardiol* 2017;40(10):797-806.

170. Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360(24):2503-15.

171. Fleurence RL, Hollenbeak CS. Rates and probabilities in economic modelling: transformation, translation and appropriate application. *Pharmacoeconomics* 2007;25(1):3-6.

172. Chaitman BR, Alexander KP, Cyr DD, et al. Myocardial Infarction in the ISCHEMIA Trial: Impact of Different Definitions on Incidence, Prognosis, and Treatment Comparisons. *Circulation* 2021;143(8):790-804.

173. Meyer K, Simmet A, Arnold M, et al. Stroke events, and case fatalities in Switzerland based on hospital statistics and cause of death statistics. *Swiss Med Wkly* 2009;139(5-6):65-9.

174. De Luca L, Uguccioni M, Meessen J, et al. External applicability of the ISCHEMIA trial: an analysis of a prospective, nationwide registry of patients with stable coronary artery disease. *EuroIntervention* 2020;16(12):e966-e73.

175. Meier D, Mahendiran T, Fournier S. Letter: Applicability of ISCHEMIA in real-world practice: where to START? *EuroIntervention* 2021;17(2):e181-e82.

176. Meier D, Mahendiran T, Fournier S. Will ISCHEMIA change our daily practice? *Cardiovasc Diagn Ther* 2020;10(4):908-11.

177. Spertus JA, Jones PG, Maron DJ, et al. Health-Status Outcomes with Invasive or Conservative Care in Coronary Disease. *N Engl J Med* 2020;382(15):1408-19.

178. Wijeysundera HC, Tomlinson G, Norris CM, et al. Predicting EQ-5D utility scores from the Seattle Angina Questionnaire in coronary artery disease: a mapping algorithm using a Bayesian framework. *Med Decis Making* 2011;31(3):481-93.

179. Wijeysundera HC, Farshchi-Zarabi S, Witteman W, et al. Conversion of the Seattle Angina Questionnaire into EQ-5D utilities for ischemic heart disease: a systematic review and catalog of the literature. *Clinicoecon Outcomes Res* 2014;6:253-68.

180. Thomas M, Jones PG, Arnold SV, et al. Interpretation of the Seattle Angina Questionnaire as an Outcome Measure in Clinical Trials and Clinical Care: A Review. *JAMA Cardiol* 2021;6(5):593-99.

181. Spinka F, Aichinger J, Wallner E, et al. Functional status and life satisfaction of patients with stable angina pectoris in Austria. *BMJ Open* 2019;9(9):e029661.

182. Matza LS, Stewart KD, Gandra SR, et al. Acute and chronic impact of cardiovascular events on health state utilities. *BMC Health Serv Res* 2015;15:173.

183. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7. *Value Health* 2012;15(6):843-50.

184. Boeddinghaus J, Gaemperli O, Meier P, et al. The SWISS PCI Survey – coronary and structural heart interventions in Switzerland 2020. *Cardiovascular Medicine* 2022;25:w10133.

185. Wagener M, Boeddinghaus J, Gaemperli O, et al. Trends in Coronary and Structural Heart Interventions in Switzerland over the Last 16 Years and Impact of COVID-19: Insights from the National Swiss PCI Survey. *J Clin Med* 2022;11(24)

186. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;79(2):e21-e129.

187. Lerman TT, Witberg G, Kornowski R. A meta-analysis of randomized controlled trials comparing percutaneous coronary intervention with optimal medical therapy in stable obstructive coronary artery disease. *Coron Artery Dis* 2021;32(7):618-24.

188. Laukkanen JA, Kunutsor SK, Lavie CJ. Percutaneous Coronary Intervention Versus Medical Therapy in the Treatment of Stable Coronary Artery Disease: An Updated Meta-Analysis of Contemporary Randomized Controlled Trials. *J Invasive Cardiol* 2021;33(8):E647-E57.

189. Shah N, Hajouli S. Transmyocardial Laser Extravascular Angiogenesis. *StatPearls Publishing* 2021;01:01.

190. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7(27):iii-x, 1-173.

191. Montori VM, Smieja M, Guyatt GH. Publication bias: a brief review for clinicians. *Mayo Clin Proc* 2000;75(12):1284-8.

192. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *Bmj* 1999;319(7211):670-4.

193. Gray AM, Clarke PM, Wolstenholme JL, et al. Applied Methods of Cost-effectiveness Analysis in Health Care. Oxford, United Kingdom: Oxford University Press 2011.

14 Appendix A: Sources of literature (databases)

14.1 Literature sources

Table 58 Biomedical bibliographic databases

Source	Website
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
Embase	https://www.embase.com/
The Cochrane Library (inc. CENTRAL)	https://www.cochranelibrary.com/
International Network of Agencies for Health Technology Assessment (INAHTA)	https://database.inahta.org/
Econlit	https://www.aeaweb.org/econlit/

Table 59 Clinical trial registries

Source	Website
ClinicalTrials.gov	https://clinicaltrials.gov
EU clinical trials registry	https://www.clinicaltrialsregister.eu
Australia New Zealand clinical trials registry (ANZCTR)	https://anzctr.org.au

Table 60 Grey literature sources

Source	Website
American College of Cardiology	www.acc.org
Australian Heart Foundation	www.heartfoundation.org.au
Austrian Cardiology Society [Österreichiche Kardiologie Gesellchaft]	www.atcardio.at
Cardiac society of Australia and New Zealand	www.csanz.edu.au
European Association for Cardio-Thoracic Surgery	www.eacts.org
European Medicines Agency	www.ema.europa.eu
European Society of Cardiology	www.escardio.org
Federal Statistical Office	www.bfs.admin.ch/bfs/en/home.html
French Society of Cardiology [Société Française de Cardiologie]	www.fcardio.fr
German Society for Cardiology [Deutche Gesellchaft für Kardiologie]	www.dgk.org
Google	www.google.com
The Italian Federation of Cardiology	www.federcardio.it
NHS Pathways	www.nhspathways.org
National Heart, Lung and Blood Institute	www.nhlbi.nih.gov
NPS Medicinewise	www.nps.org.au
Swiss Society of Cardiology [Schweizerche Gesellschaft	www.swisscardio.ch

für Kardiologie]	
Trip Database	www.tripdatabase.com
World heart federation	www.world-heart-federation.org
HTA websites of INAHTA members	
Australia	
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips
Austria	
Austrian Institute for Health Technology Assessment (AIHTA)	https://aihta.at/page/homepage/en
Gesundheit Österreich GmbH (GOG)	http://www.goeg.at
Argentina	
Institute for Clinical Effectiveness and Health Policy (IECS)	http://www.iecs.org.ar
Belgium	
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be
Brazil	
National Committee for Technology Incorporation (CONITEC)	http://conitec.gov.br/en/
Agência Nacional de Saúde Suplementar/ National Regulatory Agency for Private Health Insurance and Plans (ANS)	https://www.gov.br/ans/pt-br
Canada	
Institute of Health Economics (IHE)	http://www.ihe.ca
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/
Ontario Health (OH)	https://www.ontariohealth.ca/
Colombia	
Instituto de Evaluación Tecnológica en Salud (IETS)	http://www.iets.org.co
Denmark	
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net
Finland	
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx
France	
French National Authority for Health (Haute Autorité de Santé; HAS)	http://www.has-sante.fr/

Assistance Publique – Hôpitaux de Paris	http://cedit.aphp.fr
Germany	
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	https://www.g-ba.de/english/
Ireland	
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie
Italy	
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/
HTA Unit in A. Gemelli Teaching Hospital (UVT)	https://www.policlinicogemelli.it/
National Agency for Regional Health services (Agenas)	http://www.agenas.it
Kazakhstan	
Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development (RCHD)	http://www.rcrz.kz
Korea	
National Evidence-based healthcare Collaborating Agency (NECA)	www.neca.re.kr/eng
Malaysia	
Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAS)	http://www.moh.gov.my
The Netherlands	
The Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/
Norway	
The Norwegian Institute of Public Health (NIPHNO)	http://www.fhi.no/
Peru	
Institute of Health Technology Assessment and Research (IETSI)	http://www.essalud.gob.pe/ietsi/
Poland	
Agency for Health Technology Assessment and Tariff System (AOTMiT)	http://www.aotm.gov.pl
Republic of China, Taiwan	
Center for Drug Evaluation (CDE)	http://www.cde.org.tw
Russian Federation	
Center for Healthcare Quality Assessment and Control (CHQAC)	www.rosmedex.ru
Singapore	
Agency for Care Effectiveness (ACE)	Agency for Care Effectiveness (ACE) (ace-hta.gov.sg)

Spain	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/
Agency for Health Quality and Assessment of Catalonia (AQuAS)	http://aquas.gencat.cat
Andalusian HTA Agency	http://www.aetsa.org/
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es
Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/
Sweden	
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
Switzerland	
Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta
Tunisia	
INEAS – National Authority for Assessment and Accreditation in Healthcare, TUNISIA	http://www.ineas.tn/fr
United Kingdom	
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
Health Technology Wales (HTW)	http://www.healthtechnology.wales
National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta
United States	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html
Uruguay	
Health Assessment Division, Ministry of Public Health (HAD)	http://www.msp.gub.uy

Abbreviations:

HTA: health technology assessment; **INAHTA:** International Network of Agencies for Health Technology Assessment.

14.2 Search results

14.2.1 Systematic review results

Table 61 Summary of biomedical bibliographic database search results

Database	Results
MEDLINE	1,673
Embase (OVID)	3,632
Cochrane Library – Reviews	18
EconLit (EBSCO)	69
INAHTA	0
Grey literature searches	4
Pearling	8
Total	**6,801**

14.2.2 Efficacy, effectiveness, and safety search results

Table 62 Search strategy – MEDLINE (OVID) [15 June 2022]

No.	Query	Results
1	Coronary.mp.	540,575
2	CAD.mp.	46,987
3	((Coronary or CAD) and (obstruction or occlusion or occluded or stenosis or stenoses or lesion or "syndrome X" or microvascular disease*)).mp.	95,783
4	"Coronary artery disease*".tw.	93,048
5	"Stable coronary disease*".mp.	473
6	("tandem lesion*" or "bifurcation lesion*" or "atherosclerotic lesion*" or "coronary artery lesion*").mp.	19,446
7	"Single vessel disease".mp.	1,560
8	"Multivessel disease".mp.	3,027
9	"Stable coronary artery disease*".mp.	3,881
10	"Stable ischemic heart disease*".mp.	593
11	"Chronic ischemic heart disease*".tw.	944
12	"Coronary heart disease*".tw.	53,191
13	"Atherosclerotic heart disease*".mp.	787
14	"Nonobstructive coronary artery disease*".mp.	232
15	"Obstructive coronary artery disease*".mp.	2323
16	Atherosclero*.tw.	163,948

17	"Cardiovascular disease*".tw.	199,158
18	"chronic coronary syndrome*".mp.	553
19	"stable angina".tw.	8434
20	"after myocardial infarction*".mp.	13,531
21	(after and "anterior myocardial infarction*").mp.	1228
22	(after and "posterior myocardial infarction*").mp.	87
23	"Myocardial ischemia*".mp.	61,647
24	"myocardial ischaemia*".mp.	5,548
25	"Stable ischaemic heart disease*".mp.	87
26	**3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25**	**574,349**
27	PTCA.mp.	6,578
28	CABG.mp.	20,293
29	PCI.mp.	31,468
30	"Coronary intervention*".tw.	42,537
31	"Percutaneous coronary intervention*".tw.	39,154
32	"Percutaneous transluminal coronary angioplasty".mp.	6,757
33	"Percutaneous coronary angioplasty".mp.	708
34	Angioplast*.tw.	45,528
35	"Multivessel angioplasty*".mp.	60
36	"Artery angioplasty*".mp.	927
37	"coronary angioplasty*".mp.	13,233
38	"Balloon angioplasty*".mp.	9241
39	"Myocardial revascularisation*".tw.	397
40	"Myocardial revascularization*".tw.	4671
41	"Artery bypass grafting*".tw.	24,662
42	"Coronary artery bypass*".tw.	43,739
43	"Coronary artery bypass graft*".tw.	35,328
44	Angiograph*.tw.	199,485
45	Coronary.tw. and (START or TOSCA or RAVEL or WIDEST or ELUTES or APPLAUSE or TAXUS or SIRIUS or SCANDSTENT or DELIVER or SWISSI or RITA or GISSOC or DESTINI or SISCA or LASMAL or OCBAS or C-SIRIUS or ESIRIUS or GISSOC or PRISON or BENESTENT or DEBATE or TOAT or STOP or ADVANCE or SARECCO or SICCO or MAJIC or Compare-Acute or HAMBRECHT or COURAGE or "BARI 2D" or "FAME II" or DANAMI-3-	11,268

	PRIMULTI or OAT or DECOPI or JSAP or ISCHEMIA or EXACT or AWESOME).ti.	
46	"drug-eluting stents".tw.	7,945
47	"coronary stent*".mp.	7,773
48	"expandable stent*".mp.	1,596
49	"*coated stent*".mp.	969
50	"*eluting stent*".mp.	18,880
51	"*encapsulated stent*".mp.	10
52	"off pump bypass*".mp.	155
53	"Bare metal stent*".mp.	4846
54	**27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53**	**331,994**
55	"Optimal medical therap*".tw.	17,09
56	"Optimal medical treatment*".tw.	641
57	"Medical therap*".tw.	34,702
58	"Medical treatment*".tw.	55,960
59	OMT.mp.	1,630
60	"Lipid-lowering therap*".mp.	4,022
61	"Anti-ischemic drug*".mp.	184
62	Statin*.tw.	48,377
63	**55 or 56 or 57 or 58 or 59 or 60 or 61 or 62**	**138,800**
64	**26 and 54 and 63**	**5,434**
65	**64 not (exp animals/ not humans/)**	**5,407**
66	**limit 65 to (yr="2010 -Current" and (english or french or german or italian))**	**2,893**
67	letter.pt.	1,183,332
68	editorial.pt.	608,089
69	congress.pt.	67,101
70	news.pt.	212,949
71	**67 or 68 or 69 or 70**	**2,066,934**
72	**66 not 71**	**1,673**

Table 63 Search strategy – Embase (OVID) [15 June 2022]

No.	Query	Results
1	Coronary.mp.	662,785
2	CAD.mp.	77,136
3	((Coronary or CAD) and (obstruction or occlusion or occluded or stenosis or stenoses or lesion or "syndrome X" or microvascular disease*)).mp.	155,689
4	"Coronary artery disease*".tw.	131,183
5	"Stable coronary disease*".mp.	785
6	("tandem lesion*" or "bifurcation lesion*" or "atherosclerotic lesion*" or "coronary artery lesion*").mp.	25,702
7	"Single vessel disease".mp.	1,939
8	"Multivessel disease".mp.	4,644
9	"Stable coronary artery disease*".mp.	6,514
10	"Stable ischemic heart disease*".mp.	916
11	"Chronic ischemic heart disease*".tw.	860
12	"Coronary heart disease*".tw.	59,319
13	"Atherosclerotic heart disease*".mp.	953
14	"Nonobstructive coronary artery disease*".mp.	390
15	"Obstructive coronary artery disease*".mp.	4,169
16	Atherosclero*.tw.	201,821
17	"Cardiovascular disease*".tw.	275,286
18	"chronic coronary syndrome*".mp.	815
19	"stable angina".tw.	11,361
20	"after myocardial infarction*".mp.	15,009
21	(after and "anterior myocardial infarction*").mp.	2,006
22	(after and "posterior myocardial infarction*").mp.	115
23	"Myocardial ischemia*".mp.	36,410
24	"myocardial ischaemia*".mp.	5,444
25	"Stable ischaemic heart disease*".mp.	111
26	**3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25**	**723,892**
27	PTCA.mp.	7,222
28	CABG.mp.	35,263

29	PCI.mp.	68,092
30	"Coronary intervention*".tw.	72,716
31	"Percutaneous coronary intervention*".tw.	66,884
32	"Percutaneous transluminal coronary angioplasty".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	5101
33	"Percutaneous coronary angioplasty".mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	967
34	Angioplast*.tw	51,804
35	"Multivessel angioplasty*".mp.	45
36	"Artery angioplasty*".mp.	1,198
37	"coronary angioplasty*".mp.	27,144
38	"Balloon angioplasty*".mp.	11,737
39	"Myocardial revascularisation*".tw.	418
40	"Myocardial revascularization*".tw.	4321
41	"Artery bypass grafting*".tw.	29,529
42	"Coronary artery bypass*".tw.	52,382
43	Coronary artery bypass graft*".tw.	43,500
44	Angiograph*.tw.	232,967
45	Coronary.tw. and (START or TOSCA or RAVEL or WIDEST or ELUTES or APPLAUSE or TAXUS or SIRIUS or SCANDSTENT or DELIVER or SWISSI or RITA or GISSOC or DESTINI or SISCA or LASMAL or OCBAS or C-SIRIUS or ESIRIUS or GISSOC or PRISON or BENESTENT or DEBATE or TOAT or STOP or ADVANCE or SARECCO or SICCO or MAJIC or Compare-Acute or HAMBRECHT or COURAGE or "BARI 2D" or "FAME II" or DANAMI-3-PRIMULTI or OAT or DECOPI or JSAP or ISCHEMIA or EXACT or AWESOME).ti.	11,749
46	"drug-eluting stents".tw.	13,991
47	"coronary stent*".mp.	36890
48	"expandable stent*".mp.	2,577
49	"*coated stent*".mp.	1,427
50	"*eluting stent*".mp.	38,218
51	"*encapsulated stent*".mp.	12
52	"off pump bypass*".mp.	202
53	"Bare metal stent*".mp.	15,213
54	**27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or**	**434,746**

	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53	
55	"Optimal medical therap*".tw.	3,521
56	Optimal medical treatment*".tw.	1,369
57	"Medical therap*".tw.	49,741
58	"Medical treatment*".tw.	70,423
59	OMT.mp.	2,503
60	"Lipid-lowering therap*".mp.	6,361
61	"Anti-ischemic drug*".mp.	208
62	Statin*.tw.	78,779
63	**55 or 56 or 57 or 58 or 59 or 60 or 61 or 62**	**197,693**
64	**26 and 54 and 63**	**10,043**
65	**64 not (exp animals/ not humans/)**	**60,96**
66	**limit 65 to (yr="2010 -Current" and (english or french or german or italian))**	**3,862**
67	letter.pt.	943,940
68	editorial.pt.	640,730
69	**67 or 68**	**1,584,670**
70	**66 not 69**	**3,632**

Table 64 Search strategy – Cochrane Library [16 June 2022]

No.	Query	Results
1	Coronary:ti,ab,kw	61,258
2	CAD:ti,ab,kw	5,479
3	((Coronary or CAD) and (obstruction or occlusion or occluded or stenosis or stenoses or lesion or "syndrome X" or microvascular disease*)):ti,ab,kw	10,787
4	"Coronary artery disease*":ti,ab	12,442
5	"Stable coronary disease*":ti,ab,kw	170
6	("tandem lesion*" or "bifurcation lesion*" or "atherosclerotic lesion*" or "coronary artery lesion*"):ti,ab,kw	419
7	"Single vessel disease":ti,ab,kw	135
8	"Multivessel disease":ti,ab,kw	619
9	"Stable coronary artery disease*":ti,ab,kw	1,244
10	"Stable ischemic heart disease*":ti,ab,kw	185
11	"Chronic ischemic heart disease*":ti,ab	271
12	"Coronary heart disease*":ti,ab	7,656
13	"Atherosclerotic heart disease*":ti,ab,kw	336
14	"Nonobstructive coronary artery disease*":ti,ab,kw	62
15	"Obstructive coronary artery disease*":ti,ab,kw	260
16	Atherosclero*:ti,ab	11,480
17	"Cardiovascular disease*":ti,ab	18,783
18	"chronic coronary syndrome*":ti,ab,kw	33
19	"stable angina":ti,ab	2,992
20	"after myocardial infarction*":ti,ab,kw	1,671
21	(after and "anterior myocardial infarction*"):ti,ab,kw	260
22	(after and "posterior myocardial infarction*"):ti,ab,kw	7
23	"Myocardial ischemia*":ti,ab,kw	6,778
24	"myocardial ischaemia*":ti,ab,kw	6,778
25	"Stable ischaemic heart disease*":ti,ab,kw	185
26	**#3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25**	**59,069**
27	PTCA:ti,ab,kw	1,165
28	CABG:ti,ab,kw	5,938

29	PCI:ti,ab,kw	9,350
30	"Coronary" intervention*:ti,ab	22,599
31	"Percutaneous coronary intervention*":ti,ab	9,037
32	"Percutaneous transluminal coronary angioplasty":ti,ab,kw	875
33	"Percutaneous coronary angioplasty":ti,ab,kw	122
34	Angioplast*:ti,ab	6,269
35	"Multivessel angioplasty*":ti,ab,kw	9
36	"Artery angioplasty*":ti,ab,kw	65
37	"coronary angioplasty*":ti,ab,kw	2,558
38	"Balloon angioplasty*":ti,ab,kw	1,308
39	"Myocardial revascularization*":ti,ab	575
40	"Myocardial revascularisation*":ti,ab	56
41	"Artery bypass grafting*":ti,ab	4,816
42	"Coronary artery bypass*":ti,ab	9,469
43	"Coronary artery bypass graft*":ti,ab	3,360
44	Angiograph*:ti,ab	16,196
45	Coronary:ti,ab AND (START OR TOSCA OR RAVEL OR WIDEST OR ELUTES OR APPLAUSE OR TAXUS OR SIRIUS OR SCANDSTENT OR DELIVER OR SWISSI OR RITA OR GISSOC OR DESTINI OR SISCA OR LASMAL OR OCBAS OR C-SIRIUS OR ESIRIUS OR GISSOC OR PRISON OR BENESTENT OR DEBATE OR TOAT OR STOP OR ADVANCE OR SARECCO OR SICCO OR MAJIC OR Compare-Acute OR HAMBRECHT OR COURAGE OR "BARI 2D" OR "FAME II" OR "DANAMI-3-PRIMULTI" OR OAT OR DECOPI OR JSAP OR ISCHEMIA OR EXACT OR AWESOME):ti	1,411
46	"drug-eluting stents":ti,ab	1,815
47	"coronary stent*":ti,ab,kw	2,156
48	"expandable stent*":ti,ab,kw	86
49	"*coated stent*":ti,ab,kw	153
50	"*eluting stent*":ti,ab,kw	3,429
51	"*encapsulated stent*":ti,ab,kw	11
52	"off pump bypass*":ti,ab,kw	22
53	"Bare metal stent*":ti,ab,kw	942
54	**#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53**	**48,823**
55	"Optimal medical therap*":ti,ab	0

56	"Optimal medical treatment*":ti,ab	218
57	"Medical therap*":ti,ab	1
58	"Medical treatment*":ti,ab	6,701
59	OMT:ti,ab,kw	546
60	"Lipid-lowering therap*":ti,ab,kw	0
61	"Anti-ischemic drug*":ti,ab,kw	24
62	Statin*:ti,ab	10,509
63	**#55 or #56 or #57 or #58 or #59 or #60 or #61 or #62**	**17,627**
64	**#26 and #54 and #63 in Publications**	**1,566**
Filtered		
65	**#64 in Cochrane Reviews**	**18**
66	**#64 in Cochrane Protocols**	**0**

Table 65 Search strategy – INAHTA database [29 June 2022]

No.	Query	Results
1	("CCS" OR IHD OR "Ischemic heart disease" OR "Ischaemic heart disease" OR "Coronary artery disease" OR Atherosclerosis OR) AND (CABG OR Coronary AND bypass OR PCI OR "Percutaneous coronary intervention") FROM 2010 TO 2022	0

Abbreviations
INAHTA: International network of agencies for health technology assessment

14.2.3 Economic search results

Table 66 Search strategy – EconLit (EBSCO) [29 June 2022]

No.	Query	Results
1	CCS	406
2	"coronary artery disease"	37
3	"heart disease"	306
4	Atherosclerosis	10
5	Coronary	239
6	**1 or 2 or 3 or 4 or 5**	**870**
7	Coronary angioplasty	20
8	CABG	42
9	Percutaneous coronary intervention	24

No.	Query	Results
10	PTCA	12
11	**7 or 8 or 9 or 10**	**76**
12	**6 and 11**	**69**

14.2.4 Clinical trials search results

Table 67 Search strategy – ClinicalTrials.gov [23 November 2022]

No.	Query	Results
1	CABG OR coronary artery bypass graft OR PCI OR PTCA OR coronary angioplasty OR revascularisation OR revascularization	161

Table 68 Search strategy – Australia New Zealand Clinical Trials Registry (ANZCTR) [23 November 2022]

No.	Query	Results
1	CCS OR chronic coronary syndrome OR chronic ischaemic heart disease chronic OR chronic ischemic heart disease OR stable ischaemic heart disease OR stable ischemic heart disease OR stable atherosclerosis	0
2	coronary artery disease OR ischaemic heart disease AND CABG OR coronary artery bypass graft	953*

Notes:
*only 387 of 953 records were accessible.

Table 69 Search strategy – EU clinical trials registry [23 November 2022]

No.	Query	Results
1	CCS OR chronic coronary syndrome OR chronic ischaemic heart disease chronic OR chronic ischemic heart disease OR stable ischaemic heart disease OR stable ischemic heart disease OR stable atherosclerosis	0
2	coronary artery disease AND CABG	128
3	coronary artery disease AND PCI OR Percutaneous Coronary Intervention	127

15 Appendix B: Evidence pertaining to effectiveness and safety outcomes

15.1 Evidence Tables: MACE

Table 70 MACE reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
12 mo						
EUROCTO, 2018[117]	X	12	PCI + OMT	259	13	0.76 (0.34, 1.74)
			OMT	137	9	
FAME 2, 2012[108]	-	7	PCI + OMT	447	19	0.33 (0.20, 0.55)
			OMT	441	56	
24 mo						
FAME 2, 2012[107]	-	24	PCI + OMT	447	36	0.41 (0.29, 0.60)
			OMT	441	86	
60 mo						
BARI 2D, 2009[114]	-	60	CABG + OMT	378	79	0.70 (0.55, 0.90)
			OMT	385	115	
			PCI + OMT	798	187	1.13 (0.94, 1.4)
			OMT	807	168	
			revascularisation + OMT	1,176	266	0.95 (0.82, 1.10)
			OMT	1,192	283	
FAME 2, 2012[118]	-	60	PCI + OMT	447	62	0.51 (0.39, 0.68)
			OMT	441	119	
ISCHEMIA, 2020[12]	X	60	revascularisation + OMT	2,588	318	0.90 (0.79, 1.04)
			OMT	2,591	352	
ISCHEMIA–CKD, 2020[104]	-	36	revascularisation + OMT	388	123	0.96 (0.78, 1.17)
			OMT	389	129	
STICH, 2011[115]	-	56	CABG + OMT	610	351	0.84 (0.77, 0.92)
			OMT	602	411	
120 mo						
STICH, 2011[116]	-	118	CABG + OMT	610	506	0.93 (0.89, 0.97)
			OMT	602	538	

Index

+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval**; MACE:** major adverse cardiac events; **mo:** month; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial; **REV:** revascularisation; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

MACE defined as all-cause mortality, MI, stroke and/or hospitalisation.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

Table 71 MACE reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)	HR (95% CI)
12 mo							
Danson et al. 2019[121]	(+)	12	PCI + OMT	54	11	0.46 (0.25, 0.84)	NR
			OMT	54	24		
60 mo							
Ladwiniec et al. 2015[123]	(+)	60	PCI + OMT	294	41	0.72 (0.50, 1.04)	0.64 (0.42, 0.99)
			OMT	294	57		
Hannan et al. 2012[122]	(+)	35	PCI + OMT	933	293	1.09 (0.95, 1.25)	NR
		34	OMT	933	269		
120 mo							
Prestipino et al. 2016[125]	(+)	79	PCI + OMT	42	6	1.46 (0.45, 4.81)	NR
		87	OMT	41	4		

Index

(+ +) = high quality; **(+)** = acceptable; **(0)** = unacceptable

Abbreviations

CI: confidence interval**; HR:** hazard ratio**; MACE:** major adverse cardiac events; **mo:** month; **NA:** not applicable; **NR:** not reported; **NRSI:** nonrandomised studies of interventions; **PCI:** percutaneous coronary intervention; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

MACE defined as all-cause mortality, MI, stroke and/or hospitalisation.

All included NRSI controlled for measured confounders.

15.2 Evidence Tables: All-cause mortality

Table 72 All-cause mortality reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
12 mo						
EUROCTO, 2018[117]	✗	12	PCI + OMT	259	2	2.65 (0.13, 54.80)
			OMT	137	0	
FAME 2, 2012[108]	-	7	PCI + OMT	447	1	0.33 (0.03, 3.15)
			OMT	441	3	
Hennigan et al. 2020[110]	-	3	PCI + OMT	52	0	0.14 (0.01, 2.70)
			OMT	52	3	
24 mo						
FAME 2, 2012[107]	-	24	PCI + OMT	447	6	0.74 (0.26, 2.12)
			OMT	441	8	
60 mo						
BARI 2D, 2009[114]	-	60	CABG + OMT	378	53	0.83 (0.59, 1.16)
			OMT	385	65	
			PCI + OMT	378	53	1.18 (0.86, 1.61)

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
			OMT	807	96	
			revascularisation + OMT	1,176	266	0.95 (0.82, 1.10)
			OMT	1,192	283	
FAME 2, 2012[118]	-	60	PCI + OMT	447	23	0.99 (0.56, 1.73)
			OMT	441	23	
ISCHEMIA, 2020[12]	X	60	revascularisation + OMT	2,588	318	0.90 (0.79, 1.04)
			OMT	2,591	352	
ISCHEMIA–CKD, 2020[104]	-	36	revascularisation + OMT	388	123	0.96 (0.78, 1.17)
			OMT	389	129	
120 mo						
STICH, 2011[116]	-	118	CABG + OMT	610	359	0.89 (0.82, 0.97)
			OMT	602	398	

Index

+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval**; mo:** month; **NA:** not applicable; **PCI:** percutaneous coronary intervention; **REV:** revascularisation; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

Table 73 All-cause mortality reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)	HR (95% CI)
12 mo							
Wijeysundera et al. 2014[126]	(+)	3	revascularisation + OMT	4,838	NR	NR	0.77 (0.68, 0.8774)
			OMT	4,838	NR		
60 mo							
Phan et al. 2021[124]	(+)	42	CABG + OMT	139	NR	NR	1.22 (0.70, 2.12)
			PCI + OMT	418	NR		0.90 (0.69. 1.18)
			revascularisation + OMT	557	NR		0.94 (0.73, 1.22)
			OMT	458	NR	NA	NA
Anderson et al. 2016[119]	(0)	25	PCI + OMT	2,503	676	0.89 (0.82, 0.97)	0.86 (0.77, 0.97)
			OMT	2,503	758		
Ladwiniec et al. 2015[123]	(+)	60	PCI + OMT	294	34	0.69 (0.46, 1.04)	0.63 (0.40, 1.00)
			OMT	294	49		
Hannan et al. 2012[122]	(+)	35	PCI + OMT	933	310	1.06 (0.93, 1.21)	NR
		34	OMT	933	292		
Wijeysundera	(+)	30	revascularisati	4,838	416	0.68 (0.60, 0.76)	NR

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)	HR (95% CI)
et al. 2014[126]			on + OMT				
			OMT	4,838	614		
120 mo							
Castleberry et al. 2014[120]	**(+)**	64	PCI + OMT	3,095	NR	NR	0.83 (0.75, 0.91)
			OMT	3,451	NR		
Prestipino et al. 2016[125]	**(+)**	79	PCI + OMT	42	6	0.40 (0.23, 0.69)	NR
		87	OMT	41	4		

Index

(+ +) = high quality; **(+)** = acceptable; **(0)** = unacceptable

Abbreviation

CABG: coronary artery bypass; **CI:** confidence interval**; HR:** hazard ratio**; MACE:** major adverse cardiac events; **mo:** month; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **PCI:** percutaneous coronary intervention; **REV:** revascularisation; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

All included NRSIs controlled for measured confounders.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

15.3 Evidence Tables: Hospitalisation

Table 74 Hospitalisation reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
12 mo						
EUROCTO, 2018[117]	X	12	PCI + OMT	259	15	0.99 (0.43, 2.28)
			OMT	137	8	
60 mo						
STICH, 2011[105]	-	56	CABG + OMT	610	290	0.84 (0.75, 0.94)
			OMT	602	340	
ISCHEMIA, 2020[12]	X	60	revascularisation + OMT	2,588	51	2.04 (1.27, 3.29)
			OMT	2,591	25	
ISCHEMIA–CKD, 2020[104]	-	36	revascularisation + OMT	388	17	0.77 (0.42, 1.44)
			OMT	389	22	
120 mo						
STICH, 2011[116]	-	118	CABG + OMT	610	349	0.90 (0.82, 0.99)
			OMT	602	383	

Index

+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval**; mo:** month; **NA:** not applicable; **NR:** not reported; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial; **REV:** revascularisation; **RR**: risk ratio; **RoB**: risk of bias

Notes
OMT assumed to be equivalent between trial arms.
Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.
Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

Table 75 Hospitalisation reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)	HR (95% CI)
12 mo							
Anderson et al. 2016[119]	**(0)**	3	PCI + OMT	2,503	705	0.93 (0.85, 1.01)	NR
			OMT	2,503	758		
60 mo							
Phan et al. 2021[124]	**(+)**	42	revascularisation + OMT	557	NR	NR	1.12 (0.96, 1.30)
			OMT	458	NR		
Hannan et al. 2012[122]	**(+)**	35	PCI + OMT	933	332	1.11 (0.98, 1.27)	NR
		34	OMT	933	298		

Index
(+ +) = high quality; **(+)** = acceptable; **(0)** = unacceptable
Abbreviation
CI: confidence interval**; HR:** hazard ratio**; mo:** month; **NA:** not applicable; **NR:** not reported; **NRSI:** nonrandomised studies of interventions; **PCI:** percutaneous coronary intervention; **REV:** revascularisation; **RR**: risk ratio; **RoB**: risk of bias
Notes
OMT assumed to be equivalent between trial arms.
All included NRSIs controlled for measured confounders.
Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.
Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

15.4 Evidence Tables: Subsequent revascularisation

Table 76 Subsequent revascularisation reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
12 mo						
EUROCTO, 2018[117]	X	12	PCI + OMT	259	7	0.41 (0.16, 1.08)
			OMT	137	9	
STICH, 2011[109]	-	12	CABG + OMT	610	55	0.84 (0.59, 1.17)
			OMT	602	65	
FAME 2, 2012[108]	-	7	PCI + OMT	447	9	0.20 (0.10, 0.40)
			OMT	441	45	
24 mo						

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
FAME 2, 2012[107]	-	24	PCI + OMT	447	36	0.20 (0.14, 0.28]
			OMT	441	179	
60 mo						
STICH, 2011[109]	-	56	CABG + OMT	610	55	0.54 (0.40, 0.74)
			OMT	602	100	
BARI 2D, 2009[106]	-	60	CABG + OMT	377	27	0.20 (0.14, 0.30)
			OMT	385	137	
			PCI + OMT	796	213	0.68 (0.59, 0.79)
			OMT	806	315	
			revascularisation + OMT	1,173	240	0.54 (0.50, 0.62)
			OMT	1,191	452	
FAME 2, 2012[118]	-	60	PCI + OMT	447	60	0.26 (0.20, 0.34)
			OMT	441	225	

Index

+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval**; mo:** month; **NA:** not applicable; **NR:** not reported; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial; **REV:** revascularisation; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

Table 77 Subsequent revascularisation reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)	HR (95% CI)
12 mo							
Wijeysundera et al. 2014[126]	(+)	3	revascularisation + OMT	4838	NR	NR	0.67 (0.63, 0.72)
			OMT	4838	NR		
60 mo							
Phan et al. 2021[124]	(+)	42	PCI + OMT	418	NR	NR	3.34 (1.74, 6.4)
			revascularisation + OMT	557	NR	NR	2.52 (1.35, 4.70)
			OMT	458	NR	NA	NA
Ladwiniec et al. 2015[123]	(+)	60	PCI + OMT	294	69	1.97 (1.36, 2.86)	1.81 (1.18, 2.97)
			OMT	294	35		
Hannan et al. 2012[122]	(+)	35	PCI + OMT	933	255	1.19 (1.01, 1.39)	NR
		34	OMT	933	215		
Wijeysundera et al. 2014[126]	(+)	30	revascularisation + OMT	4838	842	0.72 (0.67, 0.78)	NR
			OMT	4838	1166		

Index

(+ +) = high quality; **(+)** = acceptable; **(0)** = unacceptable

Abbreviation

CABG: coronary artery bypass; **CI:** confidence interval**; HR:** hazard ratio**; mo:** month; **NA:** not applicable; **NR:** not reported; **NRSI:** nonrandomised studies of interventions; **PCI:** percutaneous coronary intervention; **REV:** revascularisation; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

All included NRSIs controlled for measured confounders.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

15.5 Evidence Tables: General HRQoL

Table 78 General HRQoL reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Tool	Intervention	Sample size	Mean	SD	MD (95% CI)
12 mo								
EUROCTO, 2018[117]	X	12	EQ-5D–VAS	PCI + OMT	244	72.30	1.10	2.00 (1.69, 2.31)
				OMT	132	70.30	1.65	
STICH, 2011[115]	-	12	EQ-5D–VAS	CABG + OMT	447	69.20	17.90	3.80 (1.42, 6.18)
				OMT	455	65.40	18.50	
24 mo								
STICH, 2011[115]	-	24	EQ-5D–VAS	CABG + OMT	390	68.60	17.80	2.70 (0.17, 5.23)
				OMT	398	65.90	18.40	
60 mo								
STICH, 2011[115]	-	36	EQ-5D–VAS	CABG + OMT	384	69.00	17.90	1.90 (0.61, 4.41)
				OMT	378	67.10	17.40	

Index

+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval**; EQ-5D–VAS:** European quality of life 5-dimension questionnaire – visual analogue scale; **HRQoL:** health-related quality of life; **mo:** month; **NA:** not applicable; **PCI:** percutaneous coronary intervention; **SD:** standard deviation; **MD:** mean difference; **RCT:** randomised control trial; **REV:** revascularisation; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

15.6 Evidence Tables: Cardiac-specific HRQoL

Table 79 Cardiac-specific HRQoL reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Tool	Domain	Intervention	Sample size	Mean	SD	MD (95% CI)
12 mo									
EUROCTO, 2018[117]	X	12	SAQ	AF	PCI + OMT	232	91.80	16.30	4.20 (0.34, 8.06)
					OMT	128	87.60	18.70	
				AS	PCI + OMT	231	57.70	19.60	1.50 (-2.85, 5.85)
					OMT	125	56.20	20.20	
				PL	PCI + OMT	215	80.20	22.40	3.60 (-1.46, 8.66)
					OMT	121	76.60	22.90	
				QoL	PCI + OMT	230	76.60	23.00	4.80 (-0.57, 10.17)
					OMT	125	71.80	25.50	
				TS	PCI + OMT	230	90.00	15.30	0.80 (-2.34, 3.94)
					OMT	125	89.20	13.90	
[a] Hennigan et al. 2020 [110]	-	3	SAQ	AF	PCI + OMT	44	15.20	29.00	1.70 (-9.56, 12.96)
					OMT	45	13.50	25.00	
				AS	PCI + OMT	44	-2.80	32.00	-3.30 (-16.60, 10.00)
					OMT	45	0.50	32.00	
				PL	PCI + OMT	44	11.60	24.00	8.70 (-0.49, 17.89)
					OMT	45	2.90	20.00	
				QoL	PCI + OMT	44	18.50	24.00	5.60 (-4.37, 15.57)
					OMT	45	12.90	24.00	
				TS	PCI + OMT	44	0.90	17.00	3.20 (-3.66, 10.06)
					OMT	45	-2.30	16.00	
STICH, 2011 [111]	-	12	SAQ	AF	CABG + OMT	459	90.60	16.50	6.60 (4.05, 9.15)
					OMT	458	84.00	22.40	
				QoL	CABG + OMT	457	75.80	21.20	6.70 (3.76, 9.64)
					OMT	457	69.10	24.00	
ISCHEMIA, 2020[112]	X	12	SAQ	AF	revascularisation + OMT	828	93.76	13.75	1.80 (0.41, 3.19)
					OMT	821	91.96	14.96	
				PL	revascularisation + OMT	736	87.64	19.03	1.25 (-0.72. 3.22)
					OMT	730	86.39	19.39	
				QoL	revascularisation + OMT	816	82.36	18.94	3.56 (1.65, 5.47)
					OMT	811	78.80	20.35	
				TS	revascularisation + OMT	782	92.15	12.64	1.97 (0.66, 3.28)
					OMT	790	90.18	13.83	
24 mo									

Trial name	RoB	Timepoint of assessment (mo)	Tool	Domain	Intervention	Sample size	Mean	SD	MD (95% CI)
STICH, 2011[111]	-	24	SAQ	AF	CABG + OMT	404	90.50	17.20	4.00 (1.45, 6.55)
					OMT	403	86.50	19.70	
				QoL	CABG + OMT	401	75.50	21.50	6.80 (3.59,10.01)
					OMT	404	68.70	24.90	
ISCHEMIA, 2020[112]	X	12	SAQ	AF	revascularisation + OMT	612	94.34	13.67	1.45 (-0.11, 3.00)
					OMT	598	92.89	13.94	
				PL	revascularisation + OMT	537	87.80	18.92	1.57 (-0.74, 3.88)
					OMT	534	86.23	19.69	
				QoL	revascularisation + OMT	603	83.60	17.52	1.97 (-0.09, 4.03)
					OMT	586	81.63	18.67	
				TS	revascularisation + OMT	584	92.99	11.55	1.71 (0.30, 3.12)
					OMT	573	91.28	12.92	
60 mo									
STICH, 2011[111]	-	36	SAQ	AF	CABG + OMT	395	89.80	17.50	1.30 (-1.29, 3.89)
					OMT	372	88.50	19.00	
				QoL	CABG + OMT	395	75.30	22.10	2.40 (-0.74, 5.54)
					OMT	371	72.90	22.20	
ISCHEMIA, 2020[112]	X	36	SAQ	AF	revascularisation + OMT	409	94.46	13.68	0.82 (-1.02, 2.66)
					OMT	409	93.64	13.20	
				PL	revascularisation + OMT	363	84.98	22.21	0.18 (-3.00, 3.36)
					OMT	363	84.80	21.51	
				QoL	revascularisation + OMT	402	83.49	19.29	0.47 (-2.17, 3.11)
					OMT	394	83.02	18.72	
				TS	revascularisation + OMT	400	92.18	13.19	0.26 (-1.59, 2.11)
					OMT	393	91.92	13.36	

Index

+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations

AF: angina frequency; **AS:** anginal stability; **CABG:** coronary artery bypass; **CI:** confidence interval**; HRQoL:** health-related quality of life; **mo:** month; **NA:** not applicable; **PCI:** percutaneous coronary intervention; **PL:** physical limitation; **QoL:** quality of life; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **SMD:** standardised mean difference; **TS:** treatment satisfaction; **RCT:** randomised control trial; **REV:** revascularisation; **RoB**: risk of bias

Notes

[a] Hennigan et al. 2020 only reports SAQ domain scores as change from baseline, not as complete SAQ domain scores.

OMT assumed to be equivalent between trial arms.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

15.7 Evidence Tables: Stent thrombosis

Table 80 Stent thrombosis reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
12 mo						
EUROCTO, 2018[117]	X	12	PCI + OMT	259	1	1.59 (0.07, 38.76)
			OMT	137	0	
FAME 2, 2012[108]	-	7	PCI + OMT	447	5	4.93 (0.58, 42.05)
			OMT	441	1	
24 mo						
FAME 2, 2012[107]	-	24	PCI + OMT	447	7	3.45 (0.72, 16.53)
			OMT	441	2	
60 mo						
FAME 2, 2012[118]	-	60	PCI + OMT	447	7	3.45 (0.72, 16.53)
			OMT	441	2	

Index

+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations

CI: confidence interval**; mo:** month; **RCT:** randomised control trial; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **PCI:** percutaneous coronary intervention; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

Table 81 Stent thrombosis reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)	HR (95% CI)
60 mo							
Wijeysundera et al. 2014[126]	**(+)**	60	PCI + OMT	177	12	25.00 (1.49, 419.02)	NR
			OMT	177	0		

Index

(+ +) = high quality; **(+)** = acceptable; **(0)** = unacceptable

Abbreviations

CI: confidence interval**; HR:** hazard ratio**; mo:** month; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **PCI:** percutaneous coronary intervention; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

All included NRSI controlled for measured confounders.

15.8 Evidence Tables: MI

Table 82 MI reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
12 mo						
EUROCTO, 2018[117]	X	12	PCI + OMT	259	5	5.83 (0.32, 104.63)
			OMT	137	0	
FAME 2, 2012[108]	-	7	PCI + OMT	447	15	1.06 (0.52, 2.16)
			OMT	441	14	
24 mo						
FAME 2, 2012[107]	-	24	PCI + OMT	447	26	0.86 (0.51, 1.42)
			OMT	441	30	
60 mo						
BARI 2D, 2009[114]	-	60	revascularisation + OMT	1,176	118	0.87 (0.69, 1.09)
			OMT	1,192	138	
FAME 2, 2012[118]	-	60	PCI + OMT	447	36	0.67 (0.45, 1.00)
			OMT	441	53	
ISCHEMIA, 2020[12]	X	60	revascularisation + OMT	2,588	210	0.90 (0.75, 1.08)
			OMT	2,591	233	
ISCHEMIA–CKD, 2020[104]	-	36	revascularisation + OMT	388	46	0.82 (0.57, 1.18)
			OMT	389	56	
120 mo						
STICH, 2011[116]	-	118	CABG + OMT	610	37	0.66 (0.44, 0.99)
			OMT	602	55	

Index

+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval**; MI:** myocardial infarction; **mo:** month; **NA:** not applicable; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial; **REV:** revascularisation; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

Table 83 MI reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)	HR (95% CI)
60 mo							
Phan et al. 2021[124]	(+)	42	CABG + OMT	139	NR	NR	0.41 (0.14, 1.17)
			PCI + OMT	418	NR		1.19 (0.79, 1.79)
			revascularisation + OMT	557	NR		1.20 (0.80, 1.81)
			OMT	458	NR	NA	NA
Hannan et al. 2012[122]	(+)	35	PCI + OMT	933	332	1.11 (0.98, 1.27)	NR
		34	OMT	933	298		
Anderson et al. 2016[119]	(0)	36	PCI + OMT	2,503	140	1.40 (1.09, 1.80)	NR
			OMT	2,503	100		

Index

(+ +) = high quality; **(+)** = acceptable; **(0)** = unacceptable

Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval**; HR:** hazard ratio**; MI:** myocardial infarction; **mo:** month; **NA:** not applicable; **NR:** not reported; **NRSI:** nonrandomised studies of interventions; **PCI:** percutaneous coronary intervention; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT is assumed to be equivalent between trial arms.

All included NRSI controlled for measured confounders.

15.9 Evidence Tables: Stroke

Table 84 Stroke reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
12 mo						
EUROCTO, 2018[117]	X	12	PCI + OMT	259	2	1.06 (0.10, 11.56)
			OMT	137	1	
FAME 2, 2012[108]	-	7	PCI + OMT	447	1	0.49 (0.04, 5.42)
			OMT	441	2	
24 mo						
FAME 2, 2012[107]	-	24	PCI + OMT	447	7	1.73 (0.51, 5.86)
			OMT	441	4	
60 mo						
BARI 2D, 2009[114]	-	60	revascularisation + OMT	1,176	30	0.92 (0.57, 1.50)
			OMT	1,192	33	
FAME 2, 2012[118]	-	60	PCI + OMT	447	12	1.69 (0.67, 4.26)
			OMT	441	7	
ISCHEMIA, 2020[12]	X	60	revascularisation + OMT	2,588	45	1.18 (0.77, 1.82)
			OMT	2,591	38	

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
ISCHEMIA–CKD, 2020[104]	-	36	revascularisation + OMT	388	22	3.68 (1.51, 8.97)
			OMT	389	6	
120 mo						
STICH, 2011[116]	-	118	CABG + OMT	610	47	1.13 (0.76; 1.69)
			OMT	602	41	

Index

+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval**; mo:** month; **NA:** not applicable; **NE:** not estimable; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial; **REV:** revascularisation; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

Table 85 MI reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)	HR (95% CI)
60 mo							
Anderson et al. 2016[119]	**(0)**	36 mo	PCI + OMT	2,503	80	0.94 (0.70, 1.27)	NR
			OMT	2,503	85		

Index

(+ +) = high quality; **(+)** = acceptable; **(0)** = unacceptable

Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval**; HR:** hazard ratio**; MI:** myocardial infarction; **mo:** month; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **PCI:** percutaneous coronary intervention; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

All included NRSIs controlled for measured confounders.

15.10 Evidence Tables: Hospitalisation due to HF

Table 86 Hospitalisation due to HF reported by RCTs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)
60 mo						
STICH, 2011[116]	-	56	CABG + OMT	610	127	0.74 (0.61, 0.91)
			OMT	602	157	
ISCHEMIA, 2020[12]	X	60	revascularisation + OMT	2,588	51	2.04 (1.27, 3.29)
			OMT	2,591	25	
ISCHEMIA–CKD, 2020[104]	-	36	revascularisation + OMT	388	17	1.42 (0.69, 2.93)
			OMT	389	12	
120 mo						
STICH, 2011[116]	-	118	CABG + OMT	610	47	0.77 (0.65, 0.92)
			OMT	602	41	

Index

+ = low risk; **x** = high risk; **-** = some concerns

Abbreviations

CABG: coronary artery bypass; **CI:** confidence interval**; HF:** heart failure; **mo:** month; **NA:** not applicable; **NE:** not estimable; **PCI:** percutaneous coronary intervention; **RCT:** randomised control trial; **REV:** revascularisation; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT assumed to be equivalent between trial arms.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

15.11 Evidence Tables: Target vessel revascularisation

Table 87 Target vessel revascularisation reported by NRSIs

Trial name	RoB	Timepoint of assessment (mo)	Intervention	Sample size	Events	RR (95% CI)	HR (95% CI)
60 mo							
Wijeysundera et al. 2014[126]	**(+)**	60	PCI + OMT	177	13	27.00 (1.62, 450.71)	NR
			OMT	177	0		

Index

(+ +) = high quality; **(+)** = acceptable; **(0)** = unacceptable

Abbreviations

CI: confidence interval**; HR:** hazard ratio**; mo:** month; **NA:** not applicable; **NRSI:** nonrandomised studies of interventions; **PCI:** percutaneous coronary intervention; **RR**: risk ratio; **RoB**: risk of bias

Notes

OMT is assumed to be equivalent between trial arms.

All included NRSIs controlled for measured confounders.

16 Appendix C: List of excluded trials at full text

16.1 Incorrect comparator (k = 7)

1) Ariyaratne TV, Ademi Z, Huq M, et al. The real-world cost-effectiveness of coronary artery bypass surgery versus stenting in high-risk patients: Propensity score-matched analysis of a single-centre experience. *Appl Health Econ Health Policy* 2018;16(5):661-74.
2) Farkouh ME, Domanski M, Dangas GD, et al. Long-term survival following multivessel revascularization in patients with diabetes: The freedom follow-on study. *J Am Coll Cardiol* 2019;73(6):629-38. doi: 10.1016/j.jacc.2018.11.001
3) Freitas P, Madeira M, Raposo L, et al. Coronary artery bypass grafting versus percutaneous coronary intervention in patients with non-st-elevation myocardial infarction and left main or multivessel coronary disease. *Am J Cardiol* 2019;123(5):717-24. doi: 10.1016/j.amjcard.2018.11.052
4) Kawashima H, Serruys PW, Ono M, et al. Impact of optimal medical therapy on 10-year mortality after coronary revascularization. *J Am Coll Cardiol* 2021;78(1):27-38. doi: 10.1016/j.jacc.2021.04.087
5) Kawashima H, Takahashi K, Ono M, et al. Mortality 10 years after percutaneous or surgical revascularization in patients with total coronary artery occlusions. *J Am Coll Cardiol* 2021;77(5):529-40. doi: 10.1016/j.jacc.2020.11.055
6) Moroi M, Yamashina A, Tsukamoto K, et al. Coronary revascularization does not decrease cardiac events in patients with stable ischemic heart disease but might do in those who showed moderate to severe ischemia. *Int J Cardiol* 2012;158(2):246-52. doi: 10.1016/j.ijcard.2011.01.040
7) Windecker S, Stortecky S, Stefanini GG, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: Network meta-analysis. *Bmj* 2014;348:g3859. doi: 10.1136/bmj.g3859

16.2 Incorrect intervention (k = 20)

1) Bennell MC, Qiu F, Kingsbury KJ, et al. Determinants of variations in initial treatment strategies for stable ischemic heart disease. *Cmaj* 2015;187(10):E317-E25. doi: 10.1503/cmaj.141372
2) Coylewright M, Dick S, Zmolek B, et al. Pci choice decision aid for stable coronary artery disease: A randomized trial. *Circ Cardiovasc Qual Outcomes* 2016;9(6):767-76. doi: 10.1161/CIRCOUTCOMES.116.002641

3) Curzen N, Rana O, Nicholas Z, et al. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?: The ripcord study. *Circ Cardiovasc Interv* 2014;7(2):248-55. doi: 10.1161/CIRCINTERVENTIONS.113.000978
4) Freiheit EA, Hogan DB, Patten SB, et al. Frailty trajectories after treatment for coronary artery disease in older patients. *Circ Cardiovasc Qual Outcomes* 2016;9(3):230-8. doi: 10.1161/CIRCOUTCOMES.115.002204
5) Garg P, Wijeysundera HC, Yun L, et al. Practice patterns and trends in the use of medical therapy in patients undergoing percutaneous coronary intervention in ontario. *J Am Heart Assoc* 2014;3(4) doi: 10.1161/JAHA.114.000882
6) Gillespie P, O'Shea E, Murphy AW, et al. Relative cost-effectiveness of the sphere intervention in selected patient subgroups with existing coronary heart disease. *Eur J Health Econ* 2012;13(4):429-43. doi: 10.1007/s10198-011-0314-2
7) Hammal F, Ezekowitz JA, Norris CM, et al. Smoking status and survival: Impact on mortality of continuing to smoke one year after the angiographic diagnosis of coronary artery disease, a prospective cohort study. *BMC Cardiovasc Disord* 2014;14:133. doi: 10.1186/1471-2261-14-133
8) Heggie R, Briggs A, Stanley B, et al. Stratified medicine using invasive coronary function testing in angina: A cost-effectiveness analysis of the british heart foundation cormica trial. *Int J Cardiol* 2021;337:44-51. doi: 10.1016/j.ijcard.2021.05.016
9) Mancini GB, Hartigan PM, Bates ER, et al. Angiographic disease progression and residual risk of cardiovascular events while on optimal medical therapy: Observations from the courage trial. *Circ Cardiovasc Interv* 2011;4(6):545-52. doi: 10.1161/CIRCINTERVENTIONS.110.960062
10) Maron DJ, Boden WE, O'Rourke RA, et al. Intensive multifactorial intervention for stable coronary artery disease: Optimal medical therapy in the courage (clinical outcomes utilizing revascularization and aggressive drug evaluation) trial. *J Am Coll Cardiol* 2010;55(13):1348-58. doi: 10.1016/j.jacc.2009.10.062
11) Miller RJH, Bonow RO, Gransar H, et al. Percutaneous or surgical revascularization is associated with survival benefit in stable coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2020;21(9):961-70. doi: 10.1093/ehjci/jeaa083
12) Nolte JE, Neumann T, Manne JM, et al. Cost-effectiveness analysis of coronary artery disease screening in hiv-infected men. *Eur J Prev Cardiol* 2014;21(8):972-9. doi: 10.1177/2047487313483607
13) Nudi F, Di Belardino N, Versaci F, et al. Impact of coronary revascularization vs medical therapy on ischemia among stable patients with or suspected coronary artery disease undergoing serial

myocardial perfusion scintigraphy. *J Nucl Cardiol* 2017;24(5):1690-98. doi: 10.1007/s12350-016-0504-5

14) Reynolds HR, Picard MH, Spertus JA, et al. Natural history of patients with ischemia and no obstructive coronary artery disease: The ciao-ischemia study. *Circulation* 2021;144(13):1008-23. doi: 10.1161/CIRCULATIONAHA.120.046791
15) Shavadia JS, Southern DA, James MT, et al. Kidney function modifies the selection of treatment strategies and long-term survival in stable ischaemic heart disease: Insights from the alberta provincial project for outcomes assessment in coronary heart disease (approach) registry. *Eur Heart J Qual Care Clin Outcomes* 2018;4(4):274-82. doi: 10.1093/ehjqcco/qcx042
16) Taglieri N, Bacchi Reggiani ML, Ghetti G, et al. Risk of stroke in patients with stable coronary artery disease undergoing percutaneous coronary intervention versus optimal medical therapy: Systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2016;11(7):e0158769. doi: 10.1371/journal.pone.0158769
17) Terpenning S, Stillman A. Cost-effectiveness for imaging stable ischemic disease. *Br J Radiol* 2020;93(1113):20190764. doi: 10.1259/bjr.20190764
18) Tralhao A, Ferreira AM, Goncalves Pde A, et al. Accuracy of pooled-cohort equation and score cardiovascular risk calculators to identify individuals with high coronary atherosclerotic burden - implications for statin treatment. *Coron Artery Dis* 2016;27(7):573-9. doi: 10.1097/MCA.0000000000000398
19) Velazquez EJ, Williams JB, Yow E, et al. Long-term survival of patients with ischemic cardiomyopathy treated by coronary artery bypass grafting versus medical therapy. *Ann Thorac Surg* 2012;93(2):523-30. doi: 10.1016/j.athoracsur.2011.10.064
20) Williams B, Menon M, Satran D, et al. Patients with coronary artery disease not amenable to traditional revascularization: Prevalence and 3-year mortality. *Catheter Cardiovasc Interv* 2010;75(6):886-91. doi: 10.1002/ccd.22431

16.3 Incorrect outcome (k = 8)

1) Aikawa T, Naya M, Obara M, et al. Effects of coronary revascularization on global coronary flow reserve in stable coronary artery disease. *Cardiovasc Res* 2019;115(1):119-29. doi: 10.1093/cvr/cvy169
2) Barbato E, Toth GG, Johnson NP, et al. A prospective natural history study of coronary atherosclerosis using fractional flow reserve. *J Am Coll Cardiol* 2016;68(21):2247-55. doi: 10.1016/j.jacc.2016.08.055

3) Chun S, Qiu F, Austin PC, et al. Predictors and outcomes of routine versus optimal medical therapy in stable coronary heart disease. *Am J Cardiol* 2015;116(5):671-7. doi: 10.1016/j.amjcard.2015.05.035
4) Page BJ, Kireyev D, Boden WE. The role of revascularization versus medical therapy in patients with type 2 diabetes mellitus and coronary artery disease. *Curr Diab Rep* 2010;10(1):10-5. doi: 10.1007/s11892-009-0091-9
5) Phillips LM, Hachamovitch R, Berman DS, et al. Lessons learned from mpi and physiologic testing in randomized trials of stable ischemic heart disease: Courage, bari 2d, fame, and ischemia. *J Nucl Cardiol* 2013;20(6):969-75. doi: 10.1007/s12350-013-9773-4
6) Roth C, Goliasch G, Aschauer S, et al. Impact of treatment strategies on long-term outcome of cto patients. *Eur J Intern Med* 2020;77(pp 97-104):97-104. doi: 10.1016/j.ejim.2020.03.008
7) Vuurmans T, Er L, Sirker A, et al. Long-term patient and kidney survival after coronary artery bypass grafting, percutaneous coronary intervention, or medical therapy for patients with chronic kidney disease: A propensity-matched cohort study. *Coron Artery Dis* 2018;29(1):8-16. doi: 10.1097/MCA.0000000000000557
8) Wall BM, Hardison RM, Molitch ME, et al. High prevalence and diversity of kidney dysfunction in patients with type 2 diabetes mellitus and coronary artery disease: The bari 2d baseline data. *Am J Med Sci* 2010;339(5):401-10. doi: 10.1097/MAJ.0b013e3181d430ad

16.4 Incorrect population (k = 81)

1) Abo-Aly M, Misumida N, Backer N, et al. Percutaneous coronary intervention with drug-eluting stent versus optimal medical therapy for chronic total occlusion: Systematic review and meta-analysis. *Angiology* 2019;70(10):908-15. doi: 10.1177/0003319719858823
2) Abuzeid W, Zivkovic N, Elbaz-Greener G, et al. Association between revascularization and quality of life in patients with coronary chronic total occlusions: A systematic review. *Cardiovasc Revasc Med* 2021;25:47-54. doi: 10.1016/j.carrev.2020.10.006
3) Ahn JH, Yang JH, Song YB, et al. Impact of chronic total coronary occlusion location on long-term survival after percutaneous coronary intervention. *Rev Esp Cardiol (Engl Ed)* 2019;72(9):717-23. doi: 10.1016/j.rec.2018.07.011
4) Bangalore S, Pursnani S, Kumar S, et al. Percutaneous coronary intervention versus optimal medical therapy for prevention of spontaneous myocardial infarction in subjects with stable ischemic heart disease. *Circulation* 2013;127(7):769-81. doi: 10.1161/CIRCULATIONAHA.112.131961

5) Banning AP, Serruys P, De Maria GL, et al. Five-year outcomes after state-of-the-art percutaneous coronary revascularization in patients with de novo three-vessel disease: Final results of the syntax ii study. *Eur Heart J* 2022;43(13):1307-16. doi: 10.1093/eurheartj/ehab703
6) Bonafede MM, Johnson BH, Richhariya A, et al. Medical costs associated with cardiovascular events among high-risk patients with hyperlipidemia. *Clinicoecon Outcomes Res* 2015;7:337-45. doi: 10.2147/CEOR.S76972
7) Borges JC, Lopes N, Soares PR, et al. Five-year follow-up of angiographic disease progression after medicine, angioplasty, or surgery. *J Cardiothorac Surg* 2010;5:91. doi: 10.1186/1749-8090-5-91
8) Brandao SMG, Hueb W, Ju YT, et al. Utility and quality-adjusted life-years in coronary artery disease: Five-year follow-up of the mass ii trial. *Medicine (Baltimore)* 2017;96(50):e9113. doi: 10.1097/MD.0000000000009113
9) Budrys P, Bajoras V, Rees M, et al. Treatment of chronic total occlusion with percutaneous coronary intervention is associated with improved survival as compared to medical treatment alone: Insights from a single-centre registry. *Rev Cardiovasc Med* 2021;22(4):1629-32. doi: 10.31083/j.rcm2204169
10) Carvajal-Juarez I, Espinola-Zavaleta N, Antonio-Villa NE, et al. Optimal medical treatment vs Invasive approach in patients with significantly obstructive coronary artery disease and ischemia. *Arch Med Res* 2020;51(5):413-18. doi: 10.1016/j.arcmed.2020.04.002
11) Charytan DM, Natwick T, Solid CA, et al. Comparative effectiveness of medical therapy, percutaneous revascularization, and surgical coronary revascularization in cardiovascular risk subgroups of patients with ckd: A retrospective cohort study of medicare beneficiaries. *Am J Kidney Dis* 2019;74(4):463-73. doi: 10.1053/j.ajkd.2019.04.018
12) Cho JS, Her SH, Youn HJ, et al. Usefulness of the parameters of quantitative myocardial perfusion contrast echocardiography in patients with chronic total occlusion and collateral flow. *Echocardiography* 2015;32(3):475-82. doi: 10.1111/echo.12663
13) Choi JY, Rha SW, Choi BG, et al. Percutaneous coronary intervention for chronic total occlusion in single coronary arteries. *Tex Heart Inst J* 2021;48(2) doi: 10.14503/THIJ-19-7023
14) Choi KH, Yang JH, Song YB, et al. Long-term clinical outcomes of patients with coronary chronic total occlusion treated with percutaneous coronary intervention versus medical therapy according to presence of diabetes mellitus. *EuroIntervention* 2017;13(8):970-77. doi: 10.4244/EIJ-D-16-00737
15) Choi SY, Choi BG, Rha SW, et al. Percutaneous coronary intervention versus optimal medical therapy for chronic total coronary occlusion with well-developed collaterals. *J Am Heart Assoc* 2017;6(9) doi: 10.1161/JAHA.117.006357

16) Coutinho Storti F, Moffa PJ, Uchida AH, et al. New prognostic score for stable coronary disease evaluation. *Arq Bras Cardiol* 2011;96(5):411-8. doi: 10.1590/s0066-782x2011005000046
17) Dambrink J-HE, Debrauwere JP, van 't Hof AWJ, et al. Non-culprit lesions detected during primary pci: Treat invasively or follow the guidelines? *Eurointervention* 2010;5(8):968-75. doi: https://dx.doi.org/10.4244/
18) de Belder A, Myat A, Blaxill J, et al. Revascularisation or medical therapy in elderly patients with acute anginal syndromes: The rincal randomised trial. *EuroIntervention* 2021;17(1):67-74. doi: 10.4244/EIJ-D-20-00975
19) de Luca G, Verdoia M, Savonitto S, et al. Impact of diabetes on clinical outcome among elderly patients with acute coronary syndrome treated with percutaneous coronary intervention: Insights from the elderly acs 2 trial. *J Cardiovasc Med (Hagerstown)* 2020;21(6):453-59. doi: 10.2459/JCM.0000000000000978
20) De Luca L, Temporelli PL, Lucci D, et al. Current management and treatment of patients with stable coronary artery diseases presenting to cardiologists in different clinical contexts: A prospective, observational, nationwide study. *Eur J Prev Cardiol* 2018;25(1):43-53. doi: 10.1177/2047487317740663
21) Fan H, Zhou J, Yuan Z. Meta-analysis comparing the effect of combined omega-3+statin therapy versus statin therapy alone on coronary artery plaques. *Am J Cardiol* 2021;151(pp 15-24):15-24. doi: 10.1016/j.amjcard.2021.04.013
22) Friedel H, Delges A, Clouth J, et al. Expenditures of the german statutory health insurance system for patients suffering from acute coronary syndrome and treated with percutaneous coronary intervention. *Eur J Health Econ* 2010;11(5):449-55. doi: 10.1007/s10198-009-0181-2
23) Gada H, Kirtane AJ, Kereiakes DJ, et al. Meta-analysis of trials on mortality after percutaneous coronary intervention compared with medical therapy in patients with stable coronary heart disease and objective evidence of myocardial ischemia. *Am J Cardiol* 2015;115(9):1194-9. doi: 10.1016/j.amjcard.2015.01.556
24) Galli M, Vescovo GM, Andreotti F, et al. Impact of coronary stenting on top of medical therapy and of inclusion of periprocedural infarctions on hard composite endpoints in patients with chronic coronary syndromes: A meta-analysis of randomized controlled trials. *Minerva Cardiol Angiol* 2021;04:04. doi: 10.23736/S2724-5683.21.05645-3
25) Ghani A, Dambrink JHE, van 't Hof AWJ, et al. Treatment of non-culprit lesions detected during primary pci: Long-term follow-up of a randomised clinical trial. *Netherlands Heart Journal* 2012;20(9):347-53. doi: https://dx.doi.org/10.1007/s12471-012-0281-y
26) Gholami SS, Azar FEF, Rezapour A, et al. Cost-effectiveness of coronary artery bypass graft and percutaneous coronary intervention compared to medical therapy in patients with coronary

artery disease: A systematic review. *Heart Fail Rev* 2019;24(6):967-75. doi: 10.1007/s10741-019-09811-3

27) Gorenoi V, Hagen A. [percutaneous coronary intervention in addition to optimal medical therapy for stabile coronary artery disease - a systematic review and meta-analysis]. *Dtsch Med Wochenschr* 2014;139(20):1039-45. doi: 10.1055/s-0034-1369879
28) Hirlekar G, Libungan B, Karlsson T, et al. Percutaneous coronary intervention in the very elderly with nste-acs: The randomized 80+ study. *Scand Cardiovasc J* 2020;54(5):315-21. doi: 10.1080/14017431.2020.1781243
29) Hong M-K. The beneficial role of percutaneous coronary intervention over optimal medical therapy in elderly patients with coronary artery disease (brave), 2010.
30) Huang R, Song X, Zhang H, et al. The success of opening single chronic total occlusion lesions to improve myocardialviabilitytrial (sos-comedy): Study protocol of a prospective multicenter study. *Medicine (Baltimore)* 2018;97(16):e0443. doi: 10.1097/MD.0000000000010443
31) Iannaccone M, D'Ascenzo F, Piazza F, et al. Optimal medical therapy vs Coronary revascularization for patients presenting with chronic total occlusion: A meta-analysis of randomized controlled trials and propensity score adjusted studies. *Catheter Cardiovasc Interv* 2019;93(6):E320-E25. doi: 10.1002/ccd.28037
32) Juricic SA, Tesic MB, Galassi AR, et al. Randomized controlled comparison of optimal medical therapy with percutaneous recanalization of chronic total occlusion (comet-cto). *Int Heart J* 2021;62(1):16-22. doi: 10.1536/ihj.20-427
33) Karjalainen PP, Nammas W. Percutaneous revascularization of coronary chronic total occlusion: Toward a reappraisal of the available evidence. *J Cardiol* 2017;69(6):799-807. doi: 10.1016/j.jjcc.2016.12.006
34) Khan AA, Khalid MF, Ayub MT, et al. Outcomes of percutaneous coronary intervention versus optimal medical treatment for chronic total occlusion: A comprehensive meta-analysis. *Curr Probl Cardiol* 2021;46(3):100695. doi: 10.1016/j.cpcardiol.2020.100695
35) Khan SU, Singh M, Lone AN, et al. Meta-analysis of long-term outcomes of percutaneous coronary intervention versus medical therapy in stable coronary artery disease. *Eur J Prev Cardiol* 2019;26(4):433-36. doi: 10.1177/2047487318800511
36) Khanra D, Mishra V, Jain B, et al. Percutaneous coronary intervention provided better long term results than optimal medical therapy alone in patients with chronic total occlusion: A meta-analysis. *Indian Heart J* 2020;72(4):225-31. doi: 10.1016/j.ihj.2020.07.013
37) Khatri J, Abdallah M, Ellis S. Management of coronary chronic total occlusion. *Cleve Clin J Med* 2017;84(12 Suppl 3):27-38. doi: 10.3949/ccjm.84.s3.03

38) Kim CH, Yang JH, Park TK, et al. Revascularization vs Medical therapy for coronary chronic total occlusions in patients with chronic kidney disease. *Circ J* 2018;82(8):2136-42. doi: 10.1253/circj.CJ-17-1272

39) Kocas C, Abaci O, Oktay V, et al. Percutaneous coronary intervention vs Optimal medical therapy--the other side of the coin: Medication adherence. *J Clin Pharm Ther* 2013;38(6):476-9. doi: 10.1111/jcpt.12091

40) Kucuk U, Duygu A, Kirilmaz B. Effect of treatment regimen on long-term mortality of geriatric patients diagnosed with stable coronary artery disease. *Cureus* 2021;13(2):e13618. doi: 10.7759/cureus.13618

41) Kulik A, Shrank WH, Levin R, et al. Adherence to statin therapy in elderly patients after hospitalization for coronary revascularization. *Am J Cardiol* 2011;107(10):1409-14. doi: 10.1016/j.amjcard.2011.01.013

42) Kumar A, Doshi R, Khan SU, et al. Revascularization or optimal medical therapy for stable ischemic heart disease: A bayesian meta-analysis of contemporary trials. *Cardiovasc Revasc Med* 2022;40:42-47. doi: 10.1016/j.carrev.2021.12.005

43) Laukkanen JA, Kunutsor SK. Revascularization versus medical therapy for the treatment of stable coronary artery disease: A meta-analysis of contemporary randomized controlled trials. *Int J Cardiol* 2021;324(pp 13-21):13-21. doi: 10.1016/j.ijcard.2020.10.016

44) Laukkanen JA, Kunutsor SK, Lavie CJ. Percutaneous coronary intervention versus medical therapy in the treatment of stable coronary artery disease: An updated meta-analysis of contemporary randomized controlled trials. *J Invasive Cardiol* 2021;33(8):E647-E57.

45) Lerman TT, Witberg G, Kornowski R. A meta-analysis of randomized controlled trials comparing percutaneous coronary intervention with optimal medical therapy in stable obstructive coronary artery disease. *Coron Artery Dis* 2021;32(7):618-24. doi: 10.1097/MCA.0000000000001022

46) Li KHC, Wong KHG, Gong M, et al. Percutaneous coronary intervention versus medical therapy for chronic total occlusion of coronary arteries: A systematic review and meta-analysis. *Curr Atheroscler Rep* 2019;21(10):42. doi: 10.1007/s11883-019-0804-8

47) Liao GZ, Li YM, Bai L, et al. Revascularization vs Conservative medical treatment in patients with chronic kidney disease and coronary artery disease: A meta-analysis. *Front Cardiovasc Med* 2021;8:818958. doi: 10.3389/fcvm.2021.818958

48) Lima EG, Charytan DM, Hueb W, et al. Long-term outcomes of patients with stable coronary disease and chronic kidney dysfunction: 10-year follow-up of the medicine, angioplasty, or surgery study ii trial. *Nephrol Dial Transplant* 2020;35(8):1369-76. doi: 10.1093/ndt/gfy379

49) Lima EG, Hueb W, Gersh BJ, et al. Impact of chronic kidney disease on long-term outcomes in type 2 diabetic patients with coronary artery disease on surgical, angioplasty, or medical treatment. *Ann Thorac Surg* 2016;101(5):1735-44. doi: 10.1016/j.athoracsur.2015.10.036
50) Ma Y, Li D, Li J, et al. Percutaneous coronary intervention versus optimal medical therapy for patients with chronic total occlusion: A meta-analysis and systematic review. *J Thorac Dis* 2018;10(5):2960-67. doi: 10.21037/jtd.2018.04.140
51) Malek LA, Silva JC, Bellenger NG, et al. Late percutaneous coronary intervention for an occluded infarct-related artery in patients with preserved infarct zone viability: A pooled analysis of cardiovascular magnetic resonance studies. *Cardiol J* 2013;20(5):552-9. doi: 10.5603/CJ.2013.0141
52) Mallidi J, Atreya AR, Cook J, et al. Long-term outcomes following fractional flow reserve-guided treatment of angiographically ambiguous left main coronary artery disease: A meta-analysis of prospective cohort studies. *Catheter Cardiovasc Interv* 2015;86(1):12-8. doi: 10.1002/ccd.25894
53) Mancini GBJ, Boden WE, Brooks MM, et al. Impact of treatment strategies on outcomes in patients with stable coronary artery disease and type 2 diabetes mellitus according to presenting angina severity: A pooled analysis of three federally-funded randomized trials. *Atherosclerosis* 2018;277:186-94. doi: 10.1016/j.atherosclerosis.2018.04.005
54) Meng S, Qiu L, Wu J, et al. Two-year left ventricular systolic function of percutaneous coronary intervention vs optimal medical therapy for patients with single coronary chronic total occlusion. *Echocardiography* 2021;38(2):368-73. doi: 10.1111/echo.14976
55) Menozzi M, Piovaccari G. Procedures for chronic total occlusion: When are they recommended and when not. *Eur heart j suppl* 2020;22(Suppl L):L114-L16. doi: 10.1093/eurheartj/suaa148
56) Morino Y. A contemporary review of clinical significances of percutaneous coronary intervention for chronic total occlusions, with some japanese insights. *Cardiovasc Interv Ther* 2021;36(2):145-57. doi: 10.1007/s12928-021-00766-7
57) Nakamura M, Yamagishi M, Ueno T, et al. Modification of treatment strategy after ffr measurement: Cvit-defer registry. *Cardiovasc Interv Ther* 2015;30(1):12-21. doi: 10.1007/s12928-014-0266-4
58) Noguchi M, Ueyama H, Fujisaki T, et al. Revascularization strategies in patients with diabetes and stable ischemic heart disease: A systematic review and meta-analysis of randomized trials. *J Cardiovasc Med (Hagerstown)* 2022;23(4):242-46. doi: 10.2459/JCM.0000000000001285
59) Pontecorboli G, Lagi F, Bagli M, et al. Results of comprehensive cardiovascular diagnostic work-up in hiv positive patients. *Infez Med* 2020;28(3):397-406.

60) Pursnani S, Korley F, Gopaul R, et al. Percutaneous coronary intervention versus optimal medical therapy in stable coronary artery disease: A systematic review and meta-analysis of randomized clinical trials. *Circ Cardiovasc Interv* 2012;5(4):476-90. doi: 10.1161/CIRCINTERVENTIONS.112.970954
61) Reynolds MR, Gong T, Li S, et al. Cost-effectiveness of coronary artery bypass grafting and percutaneous coronary intervention in patients with chronic kidney disease and acute coronary syndromes in the us medicare program. *J Am Heart Assoc* 2021;10(7):e019391. doi: 10.1161/JAHA.120.019391
62) Rezende PC, Hueb W, Garzillo CL, et al. Ten-year outcomes of patients randomized to surgery, angioplasty, or medical treatment for stable multivessel coronary disease: Effect of age in the medicine, angioplasty, or surgery study ii trial. *J Thorac Cardiovasc Surg* 2013;146(5):1105-12. doi: 10.1016/j.jtcvs2012.08.015
63) Rodes-Cabau J, Bertrand OF, Larose E, et al. Five-year follow-up of the plaque sealing with paclitaxel-eluting stents vs medical therapy for the treatment of intermediate nonobstructive saphenous vein graft lesions (veleti) trial. *Can J Cardiol* 2014;30(1):138-45. doi: 10.1016/j.cjca.2013.11.002
64) Shah R, Nayyar M, Le FK, et al. A meta-analysis of optimal medical therapy with or without percutaneous coronary intervention in patients with stable coronary artery disease. *Coron Artery Dis* 2022;33(2):91-97. doi: 10.1097/MCA.0000000000001041
65) Stergiopoulos K, Boden WE, Hartigan P, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: A collaborative meta-analysis of contemporary randomized clinical trials. *JAMA Intern Med* 2014;174(2):232-40. doi: 10.1001/jamainternmed.2013.12855
66) Stergiopoulos K, Brown DL. Initial coronary stent implantation with medical therapy vs medical therapy alone for stable coronary artery disease: Meta-analysis of randomized controlled trials. *Arch Intern Med* 2012;172(4):312-9. doi: 10.1001/archinternmed.2011.1484
67) Tao T, Wang H, Wang SX, et al. Long-term outcomes of high-risk elderly male patients with multivessel coronary disease: Optimal medical therapy versus revascularization. *J Geriatr Cardiol* 2016;13(2):152-7. doi: 10.11909/j.issn.1671-5411.2015.06.020
68) Thomas S, Gokhale R, Boden WE, et al. A meta-analysis of randomized controlled trials comparing percutaneous coronary intervention with medical therapy in stable angina pectoris. *Can J Cardiol* 2013;29(4):472-82. doi: 10.1016/j.cjca.2012.07.010
69) Tomasello SD, Boukhris M, Giubilato S, et al. Management strategies in patients affected by chronic total occlusions: Results from the italian registry of chronic total occlusions. *Eur Heart J* 2015;36(45):3189-98. doi: 10.1093/eurheartj/ehv450

70) Turner D, Raftery J, Cooper K, et al. The chd challenge: Comparing four cost-effectiveness models. *Value Health* 2011;14(1):53-60. doi: 10.1016/j.jval.2010.10.009

71) van Veelen A, Elias J, van Dongen IM, et al. Percutaneous coronary intervention versus medical therapy for chronic total coronary occlusions: A systematic review and meta-analysis of randomised trials. *Neth Heart J* 2021;29(1):30-41. doi: 10.1007/s12471-020-01503-0

72) Vij A, Kassab K, Chawla H, et al. Invasive therapy versus conservative therapy for patients with stable coronary artery disease: An updated meta-analysis. *Clin Cardiol* 2021;44(5):675-82. doi: 10.1002/clc.23592

73) Volodarskiy A, Kumar S, Amin S, et al. Optimal treatment strategies in patients with chronic kidney disease and coronary artery disease. *Am J Med* 2016;129(12):1288-98. doi: 10.1016/j.amjmed.2016.06.046

74) Wang Z, Jin L, Zhou W, et al. A single-center observational study on the efficacy of percutaneous coronary intervention for ischemic heart failure: A cohort study. *Medicine (Baltimore)* 2018;97(13):e0238. doi: 10.1097/MD.0000000000010238

75) Wijeysundera HC, Nallamothu BK, Krumholz HM, et al. Meta-analysis: Effects of percutaneous coronary intervention versus medical therapy on angina relief. *Ann Intern Med* 2010;152(6):370-9. doi: 10.7326/0003-4819-152-6-201003160-00007

76) Won H, Her AY, Kim BK, et al. Percutaneous coronary intervention is more beneficial than optimal medical therapy in elderly patients with angina pectoris. *Yonsei Med J* 2016;57(2):382-7. doi: 10.3349/ymj.2016.57.2.382

77) Yan Y, Yuan F, Liu H, et al. Percutaneous coronary intervention offers survival benefit to stable patients with one single chronic total occlusion and diabetes: A propensity score-matched analysis. *Angiology* 2020;71(2):150-59. doi: 10.1177/0003319719885301

78) Yan Y, Zhang M, Yuan F, et al. Successful revascularization versus medical therapy in diabetic patients with stable right coronary artery chronic total occlusion: A retrospective cohort study. *Cardiovasc Diabetol* 2019;18(1):108. doi: 10.1186/s12933-019-0911-4

79) Yang JH, Kim BS, Jang WJ, et al. Optimal medical therapy vs Percutaneous coronary intervention for patients with coronary chronic total occlusion - a propensity-matched analysis. *Circ J* 2016;80(1):211-7. doi: 10.1253/circj.CJ-15-0673

80) Yokoyama Y, Fukuhara S, Mori M, et al. Network meta-analysis of treatment strategies in patients with coronary artery disease and low left ventricular ejection fraction. *J Card Surg* 2021;36(10):3834-42. doi: 10.1111/jocs.15850

81) Zajac P, Zycinski P, Qawoq H, et al. Outcomes of percutaneous coronary intervention in patients after previous coronary artery bypass surgery. *Kardiol Pol* 2016;74(4):322-30. doi: 10.5603/KP.a2015.0199

16.5 Incorrect publication date (k = 26)

1) Acharjee S, Boden WE, Hartigan PM, et al. Low levels of high-density lipoprotein cholesterol and increased risk of cardiovascular events in stable ischemic heart disease patients: A post-hoc analysis from the courage trial (clinical outcomes utilizing revascularization and aggressive drug evaluation). *J Am Coll Cardiol* 2013;62(20):1826-33. doi: 10.1016/j.jacc.2013.07.051
2) Alderman EL, Bourassa MG, Cohen LS, et al. Ten-year follow-up of survival and myocardial infarction in the randomized coronary artery surgery study. *Circulation* 1990;82(5):1629-46. doi: 10.1161/01.cir.82.5.1629
3) Appleton DL, Abbate A, Biondi-Zoccai GG. Late percutaneous coronary intervention for the totally occluded infarct-related artery: A meta-analysis of the effects on cardiac function and remodeling. *Catheter Cardiovasc Interv* 2008;71(6):772-81. doi: 10.1002/ccd.21468
4) Brooks MM, Frye RL, Genuth S, et al. Hypotheses, design, and methods for the bypass angioplasty revascularization investigation 2 diabetes (bari 2d) trial. *Am J Cardiol* 2006;97(12A):9G-19G. doi: 10.1016/j.amjcard.2006.02.023
5) Caruba T, Katsahian S, Schramm C, et al. Treatment for stable coronary artery disease: A network meta-analysis of cost-effectiveness studies. *PLoS One* 2014;9(6):e98371. doi: 10.1371/journal.pone.0098371
6) Chaplin S, Scuffham PA, Alon M, et al. Secondary prevention after pci: The cost-effectiveness of statin therapy in the netherlands. *Neth Heart J* 2004;12(7-8):331-36.
7) Danchin N, David P, Bourassa MG. Coronary artery surgery as a measure of vocational rehabilitation: An analysis of the working status of patients with mild angina randomly assigned to medical or surgical treatment. *Eur Heart J* 1983;4(10):687-90. doi: 10.1093/oxfordjournals.eurheartj.a061379
8) de Soyza N, Murphy ML, Bissett JK, et al. Ventricular arrhythmias in chronic stable angina pectoris with surgical or medical treatment. *Ann Intern Med* 1978;89(1):10-4. doi: 10.7326/0003-4819-89-1-10
9) Durand-Zaleski I, Dupouy P, Coste Carrie DP, et al. A tale of two countries: Costs and financial incentives for provisional stenting during percutaneous coronary intervention in france and the united states. *Eur J Health Econ* 2002;3(4):235-9. doi: 10.1007/s10198-002-0130-9
10) European Coronary Surgery Study Group. Prospective randomized study of coronary artery bypass surgery in stable angina pectoris: A progress report on survival. *Circulation* 1982;65(7 Pt 2):67-71. doi: 10.1161/01.cir.65.7.67

11) Guinn GA, Mathur VS Surgical versus medical treatment for stable angina pectoris: Prospective randomized study with 1- to 4-year follow-up. *Ann Thorac Surg* 1976;22(6):524-7. doi: 10.1016/s0003-4975(10)64469-4
12) Henderson RA, Pocock SJ, Clayton TC, et al. Seven-year outcome in the rita-2 trial: Coronary angioplasty versus medical therapy. *J Am Coll Cardiol* 2003;42(7):1161-70. doi: 10.1016/s0735-1097(03)00951-3
13) Kocevar VS, Punekar Y, Bhor M. Meta-analysis and stochastic simulation of mortality and cost savings associated with restenotic outcomes among coronary patients treated with ptca versus other treatments. *Journal of Research in Pharmaceutical Economics* 2001;11(3-4):105-24.
14) Lage MJ. Association between abciximab and length of stay in intensive care for patients undergoing percutaneous coronary intervention: A 2-stage econometric model in a naturalistic setting. *PharmacoEconomics* 2000;18(6):581-89.
15) Lee JS, Bailey MJ, Jeong J, et al. A study on the cost-effectiveness of coronary revascularization: Introducing the simultaneous mimic health status model. *Health Econ* 1997;6(6):613-23. doi: 10.1002/(sici)1099-1050(199711)6:6<613::aid-hec305>3.0.co;2-6
16) Maron DJ, Boden WE, Spertus JA, et al. Impact of metabolic syndrome and diabetes on prognosis and outcomes with early percutaneous coronary intervention in the courage (clinical outcomes utilizing revascularization and aggressive drug evaluation) trial. *J Am Coll Cardiol* 2011;58(2):131-7. doi: 10.1016/j.jacc.2011.02.046
17) Morrison DA, Sacks J. Balancing benefit against risk in the choice of therapy for coronary artery disease. Lesson from prospective, randomized, clinical trials of percutaneous coronary intervention and coronary artery bypass graft surgery. *Minerva Cardioangiol* 2003;51(5):585-97.
18) Passamani E, Davis KB, Gillespie MJ, et al. A randomized trial of coronary artery bypass surgery. Survival of patients with a low ejection fraction. *N Engl J Med* 1985;312(26):1665-71. doi: 10.1056/NEJM198506273122603
19) Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus revascularization treatment investigators. *N Engl J Med* 1999;341(2):70-6. doi: 10.1056/NEJM199907083410202
20) Ringborg A, Lindgren P, Jonsson B. The cost-effectiveness of dual oral antiplatelet therapy following percutaneous coronary intervention: A swedish analysis of the credo trial. *Eur J Health Econ* 2005;6(4):354-62.
21) RITA-2 trialists. Coronary angioplasty versus medical therapy for angina: The second randomised intervention treatment of angina (rita-2) trial. Rita-2 trial participants. *Lancet* 1997;350(9076):461-8.

22) Schomig A, Mehilli J, de Waha A, et al. A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. *J Am Coll Cardiol* 2008;52(11):894-904. doi: 10.1016/j.jacc.2008.05.051
23) Teo KK, Sedlis SP, Boden WE, et al. Optimal medical therapy with or without percutaneous coronary intervention in older patients with stable coronary disease: A pre-specified subset analysis of the courage (clinical outcomes utilizing revascularization and aggressive drug evaluation) trial. *J Am Coll Cardiol* 2009;54(14):1303-8. doi: 10.1016/j.jacc.2009.07.013
24) Varnauskas E. Survival, myocardial infarction, and employment status in a prospective randomized study of coronary bypass surgery. *Circulation* 1985;72(6 Pt 2):V90-101.
25) Varnauskas E. Twelve-year follow-up of survival in the randomized european coronary surgery study. *N Engl J Med* 1988;319(6):332-7. doi: 10.1056/NEJM198808113190603
26) Veterans Administration Coronary Artery Bypass Surgery Cooperative Study G. Eleven-year survival in the veterans administration randomized trial of coronary bypass surgery for stable angina. *N Engl J Med* 1984;311(21):1333-9. doi: 10.1056/NEJM198411223112102

16.6 Incorrect publication status (k = 3)

1) Gupta S, Belley-Cote EP, Rochwerg B, et al. Antiplatelet therapy and coronary artery bypass grafting: Protocol for a systematic review and network meta-analysis. *Medicine (Baltimore)* 2019;98(34):e16880. doi: 10.1097/MD.0000000000016880
2) Kitabata H, Kubo T, Shiono Y, et al. Comparison of clinical outcomes following percutaneous coronary intervention versus optimal medical therapy based on gray-zone fractional flow reserve in stable angina patients with intermediate coronary artery stenosis (comfortable prospective study): Study protocol for a multicenter randomized controlled trial. *Trials* 2019;20(1):84. doi: 10.1186/s13063-019-3182-1
3) Lorenzen US, Buggeskov KB, Nielsen EE, et al. Coronary artery bypass surgery + medical therapy versus medical therapy alone for ischaemic heart disease: A protocol for a systematic review with meta-analysis and trial sequential analysis. *Syst Rev* 2019;8(1):246. doi: 10.1186/s13643-019-1155-9

16.7 Incorrect publication type (k = 64)

1) Peripheral arterial disease status and cardiovascular outcomes in the bypass angioplasty revascularization investigation 2 diabetes trial. *J Am Coll Cardiol* 2010;Conference:American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention. Atlanta, GA United States. Conference Publication: (var.pagings). 55(10 SUPPL 1) (pp A156.E1464). doi: http://dx.doi.org/10.1016/S0735-1097%2810%2961465-9

2) Peripheral arterial disease progression in the bypass angioplasty revascularization investigation 2 diabetes trial. *J Am Coll Cardiol* 2010;Conference:American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention. Atlanta, GA United States. Conference Publication: (var.pagings). 55(10 SUPPL 1) (pp A156.E1462). doi: http://dx.doi.org/10.1016/S0735-1097%2810%2961463-5
3) A comparison of clinical outcomes in the bypass angioplasty revascularization investigation in type-2 diabetes mellitus (bari 2d) by type of stent implantation. *J Am Coll Cardiol* 2010;Conference:American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention. Atlanta, GA United States. Conference Publication: (var.pagings). 55(10 SUPPL 1) (pp A128.E1200). doi: http://dx.doi.org/10.1016/S0735-1097%2810%2961201-6
4) Lack of sex-based differences in outcomes in patients with type 2 diabetes and coronary artery disease treated with contemporary medical therapy with or without prompt revascularization: A report from bari 2d. *J Am Coll Cardiol* 2010;Conference:American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention. Atlanta, GA United States. Conference Publication: (var.pagings). 55(10 SUPPL 1) (pp A128.E1198). doi: http://dx.doi.org/10.1016/S0735-1097%2810%2961199-0
5) Long term impact of race/ethnicity on death, myocardial infarction and stroke among patients enrolled in the bypass angioplasty revascularization investigation of type 2 diabetes trial (bari 2d). *J Am Coll Cardiol* 2010;Conference:American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention. Atlanta, GA United States. Conference Publication: (var.pagings). 55(10 SUPPL 1) (pp A128.E1195). doi: http://dx.doi.org/10.1016/S0735-1097%2810%2961196-5
6) Percutaneous coronary intervention versus medical therapy in stable coronary artery disease: A meta-analysis. *J Am Coll Cardiol* 2010;Conference:American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention. Atlanta, GA United States. Conference Publication: (var.pagings). 55(10 SUPPL 1) (pp A121.E1136). doi: http://dx.doi.org/10.1016/S0735-1097%2810%2961137-0
7) Impact of pretreatment ischemia on therapeutic risk reduction and long-term prognosis in patients with stable angina: Results from courage trial. *J Am Coll Cardiol* 2010;Conference:American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention. Atlanta, GA United States. Conference Publication: (var.pagings). 55(10 SUPPL 1) (pp A98.E925). doi: http://dx.doi.org/10.1016/S0735-1097%2810%2960926-6

8) Revascularization improves myocardial perfusion abnormalities to a greater extent than medical therapy in patients with coronary artery disease: Insights from the nuclear cardiology databank and duke databank for cardiovascular disease. *J Am Coll Cardiol* 2010;Conference:American College of Cardiology's 59th Annual Scientific Session and i2 Summit: Innovation in Intervention. Atlanta, GA United States. Conference Publication: (var.pagings). 55(10 SUPPL 1) (pp A88.E836). doi: http://dx.doi.org/10.1016/S0735-1097%2810%2960837-6
9) Baseline characteristics of patients in the saturn study, a comparison of rosuvastatin versus atorvastatin on coronary atherosclerotic disease burden. *Atherosclerosis Supplements* 2010;Conference:78th EAS Congress. Hamburg Germany. Conference Publication: (var.pagings). 11(2) (pp 14). doi: http://dx.doi.org/10.1016/S1567-5688%2810%2970064-7
10) Intervention coronary heart disease predictors of revascularization in the cohort assigned to only initial medical treatment in the bari 2d trial. *Circulation* 2011;Conference:American Heart Association's Scientific Sessions 2011. Orlando, FL United States. Conference Publication: (var.pagings). 124(21 SUPPL. 1) (no pagination).
11) Will not receive optimized medical therapy after percutaneous coronary intervention? Analysis from japanese prospective multicenter registry. *J Am Coll Cardiol* 2011;Conference:60th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC.11. New Orleans, LA United States. Conference Publication: (var.pagings). 57(14 SUPPL. 1) (pp E1932). doi: http://dx.doi.org/10.1016/S0735-1097%2811%2961932-3
12) Real world treatment of courage-like patients. *J Am Coll Cardiol* 2011;Conference:60th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC.11. New Orleans, LA United States. Conference Publication: (var.pagings). 57(14 SUPPL. 1) (pp E1048). doi: http://dx.doi.org/10.1016/S0735-1097%2811%2961048-6
13) Meta-analysis of randomized controlled trials comparing percutaneous coronary intervention with medical therapy in patients with stable angina. *J Am Coll Cardiol* 2011;Conference:60th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC.11. New Orleans, LA United States. Conference Publication: (var.pagings). 57(14 SUPPL. 1) (pp E961). doi: http://dx.doi.org/10.1016/S0735-1097%2811%2960961-3
14) Revascularization of a chronic total occlusion by percutaneous coronary intervention is associated with a significant reduction in mortality: Insights from a 4,327 patient meta - analysis. *J Am Coll Cardiol* 2018;Conference:67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC.18. Orlando, FL United States. 71(11 Supplement 1) (no pagination). doi: http://dx.doi.org/10.1016/S0735-1097%2818%2931597-3
15) Comparison of percutaneous coronary intervention versus optimal medical therapy in the treatment of coronary total occlusion: A meta-analysis of randomized controlled trials. *J Am Coll*

Cardiol 2019;Conference:68th Annual Scientific Session of the American College of Cardiology: ACC.19. New Orleans United States. 73(9 Supplement 1) (pp 1280). doi: http://dx.doi.org/10.1016/S0735-1097%2819%2931887-X

16) Long-term impact of inducible myocardial ischemia on outcomes in ischemic cardiomyopathy: Ten-year follow-up of the stich trial. *J Am Coll Cardiol* 2020;Conference:ACC.20 - World Congress of Cardiology. Chicago United States. 75(11) (pp 193). doi: http://dx.doi.org/10.1016/S0735-1097%2820%2930820-2
17) Percutaneous coronary intervention in chronic kidney disease patients with stable obstructive coronary artery disease: A meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2021;Conference:ACC.21. Virtual, Online. 77(18 Supplement 1) (pp 60). doi: http://dx.doi.org/10.1016/S0735-1097%2821%2901419-4
18) Management and outcomes of patients with diabetes mellitus (dm) and stable ischemic heart disease (sihd): Pooled data from the ischemia and ischemia-ckd trials. *J Am Coll Cardiol* 2021;Conference:ACC.21. Virtual, Online. 77(18 Supplement 1) (pp 138). doi: http://dx.doi.org/10.1016/S0735-1097%2821%2901497-2
19) Revascularization versus medical therapy alone for stable angina in very elderly patients >80 years old. *J Am Coll Cardiol* 2021;Conference:ACC.21. Virtual, Online. 77(18 Supplement 1) (pp 84). doi: http://dx.doi.org/10.1016/S0735-1097%2821%2901443-1
20) Network meta-analysis of revascularization strategies for patients with coronary artery disease and reduced ejection fraction. *J Am Coll Cardiol* 2021;Conference:ACC.21. Virtual, Online. 77(18 Supplement 1) (pp 75). doi: http://dx.doi.org/10.1016/S0735-1097%2821%2901434-0
21) Myocardial infarction with nonobstructive coronary artery disease (minoca)-an under-recognized diagnosis. *J Am Coll Cardiol* 2022;Conference:ACC 22. Washington, DC United States. 79(9 Supplement) (pp 2966). doi: https://dx.doi.org/10.1016/S0735-1097%2822%2903957-2
22) Days alive out of hospital for patients with left ventricular dysfunction and coronary artery disease treated with coronary artery bypass surgery or medical therapy: Findings from the stich trial. *J Am Coll Cardiol* 2022;Conference:ACC 22. Washington, DC United States. 79(9 Supplement) (pp 1058). doi: https://dx.doi.org/10.1016/S0735-1097%2822%2902049-6
23) Archbold RA. Similar 5-year clinical outcomes in patients with stable coronary artery disease and myocardial ischaemia managed with an initial approach of medical therapy compared with medical therapy + percutaneous coronary intervention. *Evid Based Med* 2014;19(5):171-2. doi: 10.1136/eb-2014-101809
24) Archbold RA. Comparison between national institute for health and care excellence (nice) and european society of cardiology (esc) guidelines for the diagnosis and management of stable

angina: Implications for clinical practice. *Open Heart* 2016;3(1):e000406. doi: 10.1136/openhrt-2016-000406

25) Athyros VG, Gossios TD, Tziomalos K, et al. Is there an additional benefit from coronary revascularization in diabetic patients with acute coronary syndromes or stable angina who are already on optimal medical treatment? *Arch Med Sci* 2011;7(6):1067-75. doi: 10.5114/aoms.2011.26621
26) Augoustides JG. Advances in the management of carotid artery disease: Focus on recent evidence and guidelines. *J Cardiothorac Vasc Anesth* 2012;26(1):166-71. doi: 10.1053/j.jvca.2011.10.004
27) Barbarawi M, Al-Abdouh A, Barbarawi O, et al. Tct connect-377 initial optimal medical therapy with or without invasive strategy for stable coronary disease: A meta-analysis and systematic review. *J Am Coll Cardiol* 2020;76(17):Thirty Second Annual Symposium Transcatheter Cardiovascular Therapeutics (TCT)-Abstracts. Virtual, Online. 76(17 Supplement) (pp B162). doi: 10.1016/j.jacc.2020.09.399
28) Bergmark BA, Morrow DA. Beyond the ischemia trial: Revascularization for stable ischemic heart disease in patients with high-risk coronary anatomical features. *J Am Heart Assoc* 2021;10(1):e019974. doi: 10.1161/JAHA.120.019974
29) Borges-Neto S, Farzaneh-Far A, Shaw LK, et al. Revascularization leads to greater reduction in ischemia than medical therapy in patients with left ventricular dysfunction and stable coronary artery disease. *J Card Fail* 2010;Conference:14th Annual Scientific Meeting Heart Failure Society of America. San Diego, CA United States. Conference Publication: (var.pagings). 16(8 SUPPL. 1) (pp S113). doi: 10.1016/j.cardfail.2010.06.396
30) Brown DL. Review: Cabg or stents compared with medical therapy in stable coronary artery disease. *Ann Intern Med* 2014;161(8):JC10. doi: 10.7326/0003-4819-161-8-201410210-02010
31) Chinnaiyan KM, Akasaka T, Amano T, et al. Rationale, design and goals of the heartflow assessing diagnostic value of non-invasive ffrct in coronary care (advance) registry. *J Cardiovasc Comput Tomogr* 2017;11(1):62-67. doi: 10.1016/j.jcct.2016.12.002
32) Dahabreh IJ, Robertson SE, Tchetgen EJ, et al. Generalizing causal inferences from individuals in randomized trials to all trial-eligible individuals. *Biometrics* 2019;75(2):685-94. doi: 10.1111/biom.13009
33) Deedwania PC, Carbajal EV. Medical therapy versus myocardial revascularization in chronic coronary syndrome and stable angina. *Am J Med* 2011;124(8):681-8. doi: 10.1016/j.amjmed.2011.02.036

34) Donner-Banzhoff N. Myocardial revascularization in chronic stable coronary artery disease: A critical discussion of a recent esc-guideline. *Zeitschrift fur Allgemeinmedizin* 2011;87(1):15-20. doi: http://dx.doi.org/10.3238/zfa.2011.0015

35) Farkouh ME, Boden WE, Bittner V, et al. Risk factor control for coronary artery disease secondary prevention in large randomized trials. *J Am Coll Cardiol* 2013;61(15):1607-15. doi: 10.1016/j.jacc.2013.01.044

36) Farkouh ME, Sidhu MS, Brooks MM, et al. Impact of chronic kidney disease on outcomes of myocardial revascularization in patients with diabetes. *J Am Coll Cardiol* 2019;73(4):400-11. doi: 10.1016/j.jacc.2018.11.044

37) Farzaneh-Far A, Phillips HR, Shaw LK, et al. Greater ischemia reduction and associated improved survival with revascularization compared to medical therapy in patients with stable coronary artery disease. *J Am Coll Cardiol* 2010;Conference:22nd Annual Symposium of the Transcatheter Cardiovascular Therapeutics, TCT 2010. Washington, DC United States. Conference Publication: (var.pagings). 56(13 SUPPL. 1) (pp B89). doi: 10.1016/j.jacc.2010.08.452

38) Feldman DN. Angina relief with percutaneous coronary intervention versus medical therapy for chronic stable angina. *Evid Based Med* 2010;15(4):105-6. doi: 10.1136/ebm1095

39) Flather M, Pepper J. Acp journal club. Cabg added no benefit to medical therapy for preventing death in cad with heart failure. *Ann Intern Med* 2011;155(4):JC2-9. doi: 10.7326/0003-4819-155-4-201108160-02009

40) Fox KAA, Metra M, Morais J, et al. The myth of 'stable' coronary artery disease. *Nat Rev Cardiol* 2020;17(1):9-21. doi: 10.1038/s41569-019-0233-y

41) Group ITR, Maron DJ, Hochman JS, et al. International study of comparative health effectiveness with medical and invasive approaches (ischemia) trial: Rationale and design. *Am Heart J* 2018;201(pp 124-135):124-35. doi: 10.1016/j.ahj.2018.04.011

42) Hannan EL, Racz MJ, Gold J, et al. Adherence of catheterization laboratory cardiologists to american college of cardiology/american heart association guidelines for percutaneous coronary interventions and coronary artery bypass graft surgery: What happens in actual practice? *Circulation* 2010;121(2):267-75. doi: 10.1161/CIRCULATIONAHA.109.887539

43) Hu L, Rha S-W, Choi BG, et al. Tctap a-079 percutaneous coronary intervention versus optimal medical therapy in diabetic patients with chronic total occlusion. *J Am Coll Cardiol* 2017;69(16):22nd Cardiovascular Summit: Transcatheter Cardiovascular Therapeutics Asia Pacific, TCTAP 2017. Seoul South Korea. 69(16 Supplement 1) (pp S45). doi: 10.1016/j.jacc.2017.03.113

44) Hudson MP. Acp journal club. Review: In stable obstructive cad, pci + medical therapy (mt) does not differ from mt alone. *Ann Intern Med* 2014;160(8):JC8. doi: 10.7326/0003-4819-160-8-201404150-02008

45) Kim SH, Behnes M, Akin I. [strategy for chronic coronary syndrome - pci or optimal medical therapy]. *Ther Umsch* 2021;78(1):2-10. doi: 10.1024/0040-5930/a001230

46) Kodera S. Cost-effectiveness of percutaneous coronary intervention for stable angina in japan. *Value Health* 2018;21:ISPOR Asia Pacific 2018 to Focus on Informing Policy and Strengthening Healthcare Systems. Tokyo Japan. 21(Supplement 2) (pp S31). doi: 10.1016/j.jval.2018.07.235

47) Kodera S, Kiyosue A, Ando J, et al. Cost-effectiveness analysis of cardiovascular disease treatment in japan. *Int Heart J* 2017;58(6):847-52. doi: 10.1536/ihj.17-365

48) Koelbl CO, Nedeljkovic ZS, Jacobs AK. Coronary chronic total occlusion (cto): A review. *Reviews in Cardiovascular Medicine* 2018;19(1):33-39. doi: https://dx.doi.org/10.31083/j.rcm.2018.01.896

49) Kones R. Recent advances in the management of chronic stable angina ii. Anti-ischemic therapy, options for refractory angina, risk factor reduction, and revascularization. *Vasc Health Risk Manag* 2010;6:749-74. doi: 10.2147/vhrm.s11100

50) Marui A. Coronary-artery bypass surgery + medical therapy is associated with longer survival over 10 years than medical therapy alone in patients with ischaemic cardiomyopathy. *Evid Based Med* 2017;22(1):32. doi: 10.1136/ebmed-2016-110478

51) National Institute for Health and Care Excellence (NICE). Surveillance report 2016 – stable angina: Management (2011) nice guideline cg126: NICE, 2016:08.

52) Patel AV, Bangalore S. Challenges with evidence-based management of stable ischemic heart disease. *Curr Cardiol Rep* 2017;19(2):11. doi: 10.1007/s11886-017-0820-7

53) Rakisheva A, Marwan M, Achenbach S. The ischemia trial: Implications for non-invasive imaging. *Anatolian Journal of Cardiology* 2020;24(1):2-6. doi: https://dx.doi.org/10.14744/AnatolJCardiol.2020.82428

54) Risos L, Berkenboom G. Revascularization versus medical treatments in stable coronary artery disease: Predicting the future of novel drug therapies for stable angina. *J Cardiovasc Pharmacol* 2014;63(3):213-7. doi: 10.1097/FJC.0000000000000051

55) Rutter MK, Nesto RW. The bari 2d study: A randomised trial of therapies for type 2 diabetes and coronary artery disease. *Diab Vasc Dis Res* 2010;7(1):69-72. doi: 10.1177/1479164109354145

56) Scudeler TL, Rezende PC, Hueb W. The cost-effectiveness of strategies in coronary artery disease. *Expert Rev Pharmacoecon Outcomes Res* 2014;14(6):805-13. doi: 10.1586/14737167.2014.957681

57) Srinivas VS, Narasimhan S. Coronary artery surgery for multivessel coronary artery disease reduces 10-year risk of myocardial infarction compared with medical treatment or percutaneous coronary intervention. *Evid Based Med* 2011;16(2):50-1. doi: 10.1136/ebm1162
58) Suma H. [surgical treatment for ischemic heart failure (stich) trial]. *Nihon Rinsho* 2011;69 Suppl 9:548-50. doi: http://dx.doi.org/10.1016/j.cardfail.2011.10.006
59) Toth G, Brodmann M, Barbato E, et al. Rational and design of the intentional coronary revascularization versus conservative therapy in patients undergoing successful peripheral artery revascularization due to critical limb ischemia trial (incorporate trial). *Am Heart J* 2019;214(pp 107-112):107-12. doi: 10.1016/j.ahj.2019.05.005
60) Ujueta F, Weiss EN, Shah B, et al. Effect of percutaneous coronary intervention on survival in patients with stable ischemic heart disease. *Curr Cardiol Rep* 2017;19(2):17. doi: 10.1007/s11886-017-0821-6
61) Vaislic C. Consensus guidelines on coronary revascularization: The end of the controversy. *Sang Thromb Vaiss* 2011;23(1):18-24. doi: http://dx.doi.org/10.1684/stv.2011.0576
62) Vutthikraivit W, Elmassry M, Rattanawong P, et al. Tct-231 prognosis of percutaneous coronary intervention versus optimal medical therapy in the treatment of chronic total coronary occlusion: A systematic review and meta-analysis. *J Am Coll Cardiol* 2019;74(13):Thirty First Annual Symposium Transcatheter Cardiovascular Therapeutics (TCT). San Francisco United States. 74(13 Supplement) (pp B230). doi: 10.1016/j.jacc.2019.08.296
63) Wijeysundera HC, Qiu F, Fefer P, et al. Association between appropriateness of coronary revascularization and quality of life in patients with stable ischemic heart disease. *BMC Cardiovasc Disord* 2014;14:137. doi: 10.1186/1471-2261-14-137
64) Yau TM, Zhang T. In patients with coronary artery disease and heart failure, the addition of coronary-artery bypass grafting to medical therapy has no effect on the overall risk of death from any cause, but assessment of suitability for surgery may predict survival benefit in subgroups. *Evid Based Med* 2012;17(6):178-9. doi: 10.1136/ebmed-2012-100641

16.8 Incorrect study design (k = 30)

1) Alvarez-Contreras L, Flores-Umanzor E, Cepas-Guillen P, et al. Clinical impact of medical therapy versus revascularization in patients with chronic coronary total occlusions. *J Invasive Cardiol* 2021;33(1):E2-E8.
2) Atreya AR, Sivalingam SK, Arora S, et al. Predictors of medical management in patients undergoing elective cardiac catheterization for chronic ischemic heart disease. *Clin Cardiol* 2016;39(4):207-14. doi: 10.1002/clc.22510

3) Biscaglia S, Tebaldi M, Mele D, et al. Angina and left ventricular dysfunction: Can we 'reduce' it? *Eur heart j suppl* 2019;21(Suppl C):C28-C31. doi: 10.1093/eurheartj/suz045
4) Bittl JA, He Y, Jacobs AK, et al. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation* 2013;127(22):2177-85. doi: 10.1161/CIRCULATIONAHA.112.000646
5) Chacko L, J PH, Rajkumar C, et al. Effects of percutaneous coronary intervention on death and myocardial infarction stratified by stable and unstable coronary artery disease: A meta-analysis of randomized controlled trials. *Circ Cardiovasc Qual Outcomes* 2020;13(2):e006363. doi: 10.1161/CIRCOUTCOMES.119.006363
6) Chaitman BR, Hadid M, Laddu AA. Choice of initial medical therapy vs Prompt coronary revascularization in patients with type 2 diabetes and stable ischemic coronary disease with special emphasis on the bari 2d trial results. *Curr Opin Cardiol* 2010;25(6):597-602. doi: 10.1097/HCO.0b013e32833f0461
7) Choy-Shan A, Zinn A, Shah B, et al. Effect of rosiglitazone on survival in patients with diabetes mellitus treated for coronary artery disease. *Coron Artery Dis* 2012;23(5):354-8. doi: 10.1097/MCA.0b013e3283564897
8) Cooney MT, Kotseva K, Dudina A, et al. Determinants of risk factor control in subjects with coronary heart disease: A report from the euroaspire iii investigators. *Eur J Prev Cardiol* 2013;20(4):686-91. doi: 10.1177/2047487312445562
9) da Silva PM. Are all statins the same? Focus on the efficacy and tolerability of pitavastatin. *Am J Cardiovasc Drugs* 2011;11(2):93-107. doi: 10.2165/11591190-000000000-00000
10) Flores-Umanzor EJ, Cepas-Guillen PL, Vazquez S, et al. Survival benefit of revascularization versus optimal medical therapy alone for chronic total occlusion management in patients with diabetes. *Catheter Cardiovasc Interv* 2021;97(3):376-83. doi: 10.1002/ccd.28815
11) Flores-Umanzor EJ, Vazquez S, Cepas-Guillen P, et al. Impact of revascularization versus medical therapy alone for chronic total occlusion management in older patients. *Catheter Cardiovasc Interv* 2019;94(4):527-35. doi: 10.1002/ccd.28163
12) Gaughan J, Kobel C, Linhart C, et al. Why do patients having coronary artery bypass grafts have different costs or length of stay? An analysis across 10 european countries. *Health Economics* 2012;21:77-88.
13) Herwig A, Dehnen D, Weltermann B. Patient factors driving overuse of cardiac catheterisation: A qualitative study with 25 participants from two german teaching practices. *BMJ Open* 2019;9(4):e024600. doi: 10.1136/bmjopen-2018-024600

14) Holck EN, Winther NS, Mogensen LJH, et al. Cost-effectiveness in patients undergoing revascularization of chronic total occluded coronary arteries-a cohort study. *Front Cardiovasc Med* 2022;9:849942. doi: 10.3389/fcvm.2022.849942
15) Howard DH, Shen Y-C. Comparative effectiveness research, courage, and technological abandonment: National Bureau of Economic Research, Inc, NBER Working Papers: 17371, 2011.
16) Ishida K, Martin-Yuste V, Prat S, et al. Prognosis of patients with reduced left ventricular ejection fraction and chronic total occlusion according to treatment applied. *Cardiovasc Revasc Med* 2021;27:22-27. doi: 10.1016/j.carrev.2020.06.006
17) Khattak A, Mandel EI, Reynolds MR, et al. Percutaneous coronary intervention versus optimal medical therapy for stable angina in advanced ckd: A decision analysis. *Am J Kidney Dis* 2017;69(3):350-57. doi: 10.1053/j.ajkd.2016.07.024
18) Ko DT, Guo H, Wijeysundera HC, et al. Assessing the association of appropriateness of coronary revascularization and clinical outcomes for patients with stable coronary artery disease. *J Am Coll Cardiol* 2012;60(19):1876-84. doi: 10.1016/j.jacc.2012.06.056
19) Kohsaka S, Fukushima K, Watanabe I, et al. Contemporary management of stable coronary artery disease- implications of the ischemia trial. *Circ J* 2021;85(11):1919-27. doi: 10.1253/circj.CJ-21-0345
20) Kubo T, Takahata M, Terada K, et al. Retrospective comparison of long-term clinical outcomes between percutaneous coronary intervention and medical therapy in stable coronary artery disease with gray zone fractional flow reserve- comfortable retrospective study. *Circ J* 2018;82(12):3044-51. doi: 10.1253/circj.CJ-18-0672
21) Kwon DH, Hachamovitch R, Popovic ZB, et al. Survival in patients with severe ischemic cardiomyopathy undergoing revascularization versus medical therapy: Association with end-systolic volume and viability. *Circulation* 2012;126(11 Suppl 1):S3-8. doi: 10.1161/CIRCULATIONAHA.111.084434
22) Min JK, Berman DS, Dunning A, et al. All-cause mortality benefit of coronary revascularization vs Medical therapy in patients without known coronary artery disease undergoing coronary computed tomographic angiography: Results from confirm (coronary ct angiography evaluation for clinical outcomes: An international multicenter registry). *Eur Heart J* 2012;33(24):3088-97. doi: 10.1093/eurheartj/ehs315
23) Orsini E, Marzilli M, Zito GB, et al. Clinical outcomes of newly diagnosed, stable angina patients managed according to current guidelines. The arca (arca registry for chronic angina) registry: A prospective, observational, nationwide study. *Int J Cardiol* 2022;352(pp 9-18):9-18. doi: 10.1016/j.ijcard.2022.01.056

24) Qayyum S, Rossington JA, Chelliah R, et al. Prospective cohort study of elderly patients with coronary artery disease: Impact of frailty on quality of life and outcome. *Open Heart* 2020;7(2):09. doi: 10.1136/openhrt-2020-001314
25) Schulman-Marcus J, Lin FY, Gransar H, et al. Coronary revascularization vs Medical therapy following coronary-computed tomographic angiography in patients with low-, intermediate- and high-risk coronary artery disease: Results from the confirm long-term registry. *Eur Heart J Cardiovasc Imaging* 2017;18(8):841-48. doi: 10.1093/ehjci/jew287
26) Shinohara H, Kodera S, Kiyosue A, et al. Efficacy of fractional flow reserve-guided percutaneous cornary intervention for patients with angina pectoris. *Int Heart J* 2020;61(6):1097-106. doi: 10.1536/ihj.20-023
27) Simonsen JA, Mickley H, Johansen A, et al. Outcome of revascularisation in stable coronary artery disease without ischaemia: A danish registry-based follow-up study. *BMJ Open* 2017;7(8):e016169. doi: 10.1136/bmjopen-2017-016169
28) Skala T, Hutyra M, Vaclavik J, et al. Prediction of long-term reverse left ventricular remodeling after revascularization or medical treatment in patients with ischemic cardiomyopathy: A comparative study between spect and mri. *Int J Cardiovasc Imaging* 2011;27(3):343-53. doi: 10.1007/s10554-010-9677-1
29) Wolff G, Dimitroulis D, Andreotti F, et al. Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: A meta-analysis. *Circ Heart Fail* 2017;10(1) doi: 10.1161/CIRCHEARTFAILURE.116.003255
30) Zimmermann FM, Omerovic E, Fournier S, et al. Fractional flow reserve-guided percutaneous coronary intervention vs Medical therapy for patients with stable coronary lesions: Meta-analysis of individual patient data. *Eur Heart J* 2019;40(2):180-86. doi: 10.1093/eurheartj/ehy812

16.9 Trial data not included in analyses (k = 46)

1) Al-Mallah MH, Ahmed AI, Nabi F, et al. Outcomes of patients with moderate-to-severe ischemia excluded from the ischemia trial. *J Nucl Cardiol* 2021;29(3):1100-05. doi: 10.1007/s12350-021-02679-7
2) Andersson B, She L, Tan RS, et al. The association between blood pressure and long-term outcomes of patients with ischaemic cardiomyopathy with and without surgical revascularization: An analysis of the stich trial. *Eur Heart J* 2018;39(37):3464-71. doi: 10.1093/eurheartj/ehy438
3) Bangalore S, Maron DJ, Fleg JL, et al. International study of comparative health effectiveness with medical and invasive approaches-chronic kidney disease (ischemia-ckd): Rationale and design. *Am Heart J* 2018;205:42-52. doi: 10.1016/j.ahj.2018.07.023

4) Beohar N, Sansing VV, Davis AM, et al. Race/ethnic disparities in risk factor control and survival in the bypass angioplasty revascularization investigation 2 diabetes (bari 2d) trial. *Am J Cardiol* 2013;112(9):1298-305. doi: 10.1016/j.amjcard.2013.05.071
5) Boden WE, Stone PH. To stent or not to stent? Treating angina after ischemia-why a conservative approach with optimal medical therapy is the preferred initial management strategy for chronic coronary syndromes: Insights from the ischemia trial. *Eur Heart J* 2021;42(14):1394-400. doi: 10.1093/eurheartj/ehab069.002
6) Bonow RO, Castelvecchio S, Panza JA, et al. Severity of remodeling, myocardial viability, and survival in ischemic lv dysfunction after surgical revascularization. *JACC Cardiovasc Imaging* 2015;8(10):1121-29. doi: 10.1016/j.jcmg.2015.03.013
7) Brooks MM, Chaitman BR, Nesto RW, et al. Clinical and angiographic risk stratification and differential impact on treatment outcomes in the bypass angioplasty revascularization investigation 2 diabetes (bari 2d) trial. *Circulation* 2012;126(17):2115-24. doi: 10.1161/CIRCULATIONAHA.112.092973
8) Choudhary J, Chiu S, Bhugra P, et al. Clinical implications of the ischemia trial: Invasive vs conservative approach in stable coronary disease. *Curr Cardiol Rep* 2021;23(5):43. doi: 10.1007/s11886-021-01470-x
9) Chung MJ, Novak E, Brown DL. Effect of prompt revascularization on outcomes in diabetic patients with stable ischemic heart disease and previous myocardial infarction in the bypass angioplasty revascularization investigation 2 diabetes (bari 2d) trial. *Coron Artery Dis* 2017;28(4):301-06. doi: 10.1097/MCA.0000000000000492
10) Damluji AA, Cohen ER, Moscucci M, et al. Insulin provision therapy and mortality in older adults with diabetes mellitus and stable ischemic heart disease: Insights from bari-2d trial. *Int J Cardiol* 2017;241(pp 35-40):35-40. doi: 10.1016/j.ijcard.2017.03.048
11) Damluji AA, Pomenti SF, Ramireddy A, et al. Influence of total coronary occlusion on clinical outcomes (from the bypass angioplasty revascularization investigation 2 diabetestrial). *Am J Cardiol* 2016;117(7):1031-8. doi: 10.1016/j.amjcard.2015.12.047
12) Deja MA, Grayburn PA, Sun B, et al. Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. *Circulation* 2012;125(21):2639-48. doi: 10.1161/CIRCULATIONAHA.111.072256
13) Everett BM, Brooks MM, Vlachos HE, et al. Troponin and cardiac events in stable ischemic heart disease and diabetes. *N Engl J Med* 2015;373(7):610-20. doi: 10.1056/NEJMoa1415921
14) Farsky PS, White J, Al-Khalidi HR, et al. Optimal medical therapy with or without surgical revascularization and long-term outcomes in ischemic cardiomyopathy. *J Thorac Cardiovasc Surg* 2021 doi: 10.1016/j.jtcvs2020.12.094

15) Feldman AM, Mann DL, She L, et al. Prognostic significance of biomarkers in predicting outcome in patients with coronary artery disease and left ventricular dysfunction: Results of the biomarker substudy of the surgical treatment for ischemic heart failure trials. *Circ Heart Fail* 2013;6(3):461-72. doi: 10.1161/CIRCHEARTFAILURE.112.000185
16) Feldman AM, She L, McNamara DM, et al. Genetic variants are not associated with outcome in patients with coronary artery disease and left ventricular dysfunction: Results of the genetic substudy of the surgical treatment for ischemic heart failure (stich) trials. *Cardiology* 2015;130(2):69-81. doi: 10.1159/000368221
17) Genuth SM, Vlachos H, Brooks MM, et al. Bari 2d: A reanalysis focusing on cardiovascular events. *Mayo Clin Proc* 2019;94(11):2249-62. doi: 10.1016/j.mayocp.2019.04.015
18) Hassanabad AF, MacQueen KT, Ali I. Surgical treatment for ischemic heart failure (stich) trial: A review of outcomes. *J Card Surg* 2019;34(10):1075-82. doi: 10.1111/jocs.14166
19) Hochman JS, Reynolds HR, Bangalore S, et al. Baseline characteristics and risk profiles of participants in the ischemia randomized clinical trial. *JAMA Cardiology* 2019;4(3):273-86. doi: http://dx.doi.org/10.1001/jamacardio.2019.0014
20) Howlett JG, Stebbins A, Petrie MC, et al. Cabg improves outcomes in patients with ischemic cardiomyopathy: 10-year follow-up of the stich trial. *JACC Heart Fail* 2019;7(10):878-87. doi: 10.1016/j.jchf.2019.04.018
21) Ikeno F, Brooks MM, Nakagawa K, et al. Syntax score and long-term outcomes: The bari-2d trial. *J Am Coll Cardiol* 2017;69(4):395-403. doi: 10.1016/j.jacc.2016.10.067
22) Jolicoeur EM, Dunning A, Castelvecchio S, et al. Importance of angina in patients with coronary disease, heart failure, and left ventricular systolic dysfunction: Insights from stich. *J Am Coll Cardiol* 2015;66(19):2092-100. doi: 10.1016/j.jacc.2015.08.882
23) Jones RH, White H, Velazquez EJ, et al. Stich (surgical treatment for ischemic heart failure) trial enrollment. *J Am Coll Cardiol* 2010;56(6):490-8. doi: 10.1016/j.jacc.2009.11.102
24) Khan AA, Chung MJ, Novak E, et al. The long-term risk of smoking in diabetic patients with stable ischemic heart disease treated with intensive medical therapy and lifestyle modification. *Eur J Prev Cardiol* 2017;24(14):1506-14. doi: 10.1177/2047487317711046
25) Kim HS, Tonino PA, De Bruyne B, et al. The impact of sex differences on fractional flow reserve-guided percutaneous coronary intervention: A fame (fractional flow reserve versus angiography for multivessel evaluation) substudy. *JACC Cardiovasc Interv* 2012;5(10):1037-42. doi: 10.1016/j.jcin.2012.06.016
26) Krone RJ, Althouse AD, Tamis-Holland J, et al. Appropriate revascularization in stable angina: Lessons from the bari 2d trial. *Can J Cardiol* 2014;30(12):1595-601. doi: 10.1016/j.cjca.2014.07.748

27) MacDonald MR, She L, Doenst T, et al. Clinical characteristics and outcomes of patients with and without diabetes in the surgical treatment for ischemic heart failure (stich) trial. *Eur J Heart Fail* 2015;17(7):725-34. doi: 10.1002/ejhf.288
28) Magee MF, Tamis-Holland JE, Lu J, et al. Sex, prescribing practices and guideline recommended, blood pressure, and ldl cholesterol targets at baseline in the bari 2d trial. *Int J Endocrinol* 2015;2015:610239. doi: 10.1155/2015/610239
29) Narayan P. International study of comparative health effectiveness with medical and invasive approaches (ischemia) trial and the appropriateness of revascularization. *Indian J Thorac Cardiovasc Surg* 2020;36(6):664-67. doi: 10.1007/s12055-020-00961-w
30) Nelson AJ, Navar AM, Mulder H, et al. Association between triglycerides and residual cardiovascular risk in patients with type 2 diabetes mellitus and established cardiovascular disease (from the bypass angioplasty revascularization investigation 2 diabetes [bari 2d] trial). *Am J Cardiol* 2020;132(pp 36-43):36-43. doi: 10.1016/j.amjcard.2020.07.005
31) Newman JD, Anthopolos R, Mancini GBJ, et al. Outcomes of participants with diabetes in the ischemia trials. *Circulation* 2021;144(17):1380-95. doi: 10.1161/CIRCULATIONAHA.121.054439
32) Nicolau JC, Stevens SR, Al-Khalidi HR, et al. Does prior coronary angioplasty affect outcomes of surgical coronary revascularization? Insights from the stich trial. *Int J Cardiol* 2019;291:36-41. doi: 10.1016/j.ijcard.2019.03.029
33) Panza JA, Ellis AM, Al-Khalidi HR, et al. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. *N Engl J Med* 2019;381(8):739-48. doi: 10.1056/NEJMoa1807365
34) Panza JA, Holly TA, Asch FM, et al. Inducible myocardial ischemia and outcomes in patients with coronary artery disease and left ventricular dysfunction. *Journal of the American College of Cardiology* 2013;61(18):1860-70. doi: https://dx.doi.org/10.1016/j.jacc.2013.02.014
35) Panza JA, Velazquez EJ, She L, et al. Extent of coronary and myocardial disease and benefit from surgical revascularization in ischemic lv dysfunction [corrected]. *J Am Coll Cardiol* 2014;64(6):553-61. doi: 10.1016/j.jacc.2014.04.064
36) Panza JA, Velazquez EJ, She L, et al. Extent of coronary and myocardial disease and benefit from surgical revascularization in ischemic lv dysfunction [corrected]. *J Am Coll Cardiol* 2014;64(6):553-61. doi: 10.1016/j.jacc.2014.04.064
37) Parikh RV, Fearon WF. Physiology over angiography to determine lesion severity: The fame trials. *Interv Cardiol Clin* 2020;9(4):409-18. doi: 10.1016/j.iccl.2020.05.001
38) Perry A, Chung MJ, Novak E, et al. Development of a risk score to identify patients with type 2 diabetes mellitus and multivessel coronary artery disease who can defer bypass surgery. *Diagn Progn Res* 2019;3:3. doi: 10.1186/s41512-019-0048-7

39) Petrie MC, Jhund PS, She L, et al. Ten-year outcomes after coronary artery bypass grafting according to age in patients with heart failure and left ventricular systolic dysfunction: An analysis of the extended follow-up of the stich trial (surgical treatment for ischemic heart failure). *Circulation* 2016;134(18):1314-24. doi: 10.1161/CIRCULATIONAHA.116.024800
40) Pina IL, Zheng Q, She L, et al. Sex difference in patients with ischemic heart failure undergoing surgical revascularization: Results from the stich trial (surgical treatment for ischemic heart failure). *Circulation* 2018;137(8):771-80. doi: 10.1161/CIRCULATIONAHA.117.030526
41) Stewart RA, Szalewska D, She L, et al. Exercise capacity and mortality in patients with ischemic left ventricular dysfunction randomized to coronary artery bypass graft surgery or medical therapy: An analysis from the stich trial (surgical treatment for ischemic heart failure). *JACC Heart Fail* 2014;2(4):335-43. doi: 10.1016/j.jchf.2014.02.009
42) Stewart RAH, Szalewska D, Stebbins A, et al. Six-minute walk distance after coronary artery bypass grafting compared with medical therapy in ischaemic cardiomyopathy. *Open Heart* 2018;5(1):e000752. doi: 10.1136/openhrt-2017-000752
43) Vidal-Perez R, Bouzas-Mosquera A, Peteiro J, et al. Ischemia trial: How to apply the results to clinical practice. *World J Cardiol* 2021;13(8):237-42. doi: 10.4330/wjc.v13.i8.237
44) White HD, O'Brien SM, Alexander KP, et al. Comparison of days alive out of hospital with initial invasive vs conservative management: A prespecified analysis of the ischemia trial. *JAMA Cardiol* 2021;6(9):1023-31. doi: 10.1001/jamacardio.2021.1651
45) Wolfe NK, Mitchell JD, Brown DL. The independent reduction in mortality associated with guideline-directed medical therapy in patients with coronary artery disease and heart failure with reduced ejection fraction. *Eur Heart J Qual Care Clin Outcomes* 2021;7(4):416-21. doi: 10.1093/ehjqcco/qcaa032
46) Zembala M, Michler RE, Rynkiewicz A, et al. Clinical characteristics of patients undergoing surgical ventricular reconstruction by choice and by randomization. *J Am Coll Cardiol* 2010;56(6):499-507. doi: 10.1016/j.jacc.2010.03.054

16.10 Unable to extract data (k = 5)

***Note**: It was not possible to extract the data from these publications and it will therefore not be possible to run the required analyses.*

1) Azzalini L, Jolicoeur EM, Pighi M, et al. Epidemiology, management strategies, and outcomes of patients with chronic total coronary occlusion. *Am J Cardiol* 2016;118(8):1128-35. doi: 10.1016/j.amjcard.2016.07.023

2) Brooks MM, Chung SC, Helmy T, et al. Health status after treatment for coronary artery disease and type 2 diabetes mellitus in the bypass angioplasty revascularization investigation 2 diabetes trial. *Circulation* 2010;122(17):1690-9. doi: 10.1161/CIRCULATIONAHA.109.912642
3) Carpeggiani C, Landi P, Michelassi C, et al. Long-term prognosis in stable angina; medical treatment or coronary revascularization in patients younger than 70 years? *Int J Cardiol* 2011;148(1):43-7. doi: 10.1016/j.ijcard.2009.10.020
4) Shuvy M, Qiu F, Chee ATA, et al. Management of chronic total coronary occlusion in stable ischemic heart disease by percutaneous coronary intervention versus coronary artery bypass grafting versus medical therapy. *Am J Cardiol* 2017;120(5):759-64. doi: 10.1016/j.amjcard.2017.05.061
5) Wrobel K, Stevens SR, Jones RH, et al. Influence of baseline characteristics, operative conduct, and postoperative course on 30-day outcomes of coronary artery bypass grafting among patients with left ventricular dysfunction: Results from the surgical treatment for ischemic heart failure (stich) trial. *Circulation* 2015;132(8):720-30. doi: 10.1161/CIRCULATIONAHA.114.014932

16.11 Unavailable (k = 2)

Note: *Full texts of these publications were not available.*

1) Aslan B, Ozbek M, Aktan A, et al. Factors associated with all-cause mortality in patients with coronary artery chronic total occlusions undergoing revascularization (percutaneous coronary intervention or surgery) or medical treatment. *Kardiologiia* 2022;62(3):49-55. doi: 10.18087/cardio.2022.3.n1948
2) Humenberger M, Lang I. Treatment of the ischemic heart disease in the elderly: Optimized medical therapy versus revascularization? *J fur Kardiologie* 2013;20(9-10):278-84.

17 Appendix D: Sensitivity analyses conducted

Table 88 Results of sensitivity analyses for CABG plus OMT compared to OMT alone (RCT)

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Risk of bias due to missing outcomes											
MACE	No difference from the analysis reported in ***Section 7.4.1.1***										
All-cause mortality	No difference from the analysis reported in ***Section 7.4.3.1***										
Hospitalisation	No difference from the analysis reported in ***Section 7.4.5.1***										
Revascularisation	No difference from the analysis reported in ***Section 7.4.7.1***										
General HRQoL	No difference from the analysis reported in ***Section 7.4.9.1***										
Cardiac-specific HRQoL	No difference from the analyses reported in ***Sections 7.4.11.1.1 to 7.4.11.5.1***										
Stent thrombosis	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
MI	No difference from the analysis reported in ***Section 7.4.15.1***										
Stroke	No difference from the analysis reported in ***Section 7.4.17.1***										
Hospitalisation due to HF	No difference from the analysis reported in ***Section 7.4.19.1***										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Risk of bias due to publications bias											
MACE	No difference from the analysis reported in ***Section 7.4.1.1***										
All-cause mortality	No difference from the analysis reported in ***Section 7.4.3.1***										
Hospitalisation	No difference from the analysis reported in ***Section 7.4.5.1***										

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Revascularisation	No difference from the analysis reported in ***Section 7.4.7.1***										
General HRQoL	No difference from the analysis reported in ***Section 7.4.9.1***										
Cardiac-specific HRQoL	No difference from the analyses reported in ***Sections 7.4.11.1.1 to 7.4.11.5.1***										
Stent thrombosis	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
MI	No difference from the analysis reported in ***Section 7.4.15.1***										
Stroke	No difference from the analysis reported in ***Section 7.4.17.1***										
Hospitalisation due to HF	No difference from the analysis reported in ***Section 7.4.19.1***										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Risk of bias due to selection bias											
MACE	No difference from the analysis reported in ***Section 7.4.1.1***										
All-cause mortality	No difference from the analysis reported in ***Section 7.4.3.1***										
Hospitalisation	No difference from the analysis reported in ***Section 7.4.5.1***										
Revascularisation	No difference from the analysis reported in ***Section 7.4.7.1***										
General HRQoL	No difference from the analysis reported in ***Section 7.4.9.1***										
Cardiac-specific HRQoL	No difference from the analyses reported in ***Sections 7.4.11.1.1 to 7.4.11.5.1***										
Stent thrombosis	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
MI	No difference from the analysis reported in ***Section 7.4.15.1***										
Stroke	No difference from the analysis reported in ***Section 7.4.17.1***										
Hospitalisation due to HF	No difference from the analysis reported in ***Section 7.4.19.1***										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Imputed data											
MACE	Unable to conduct sensitivity analysis as no data was imputed by authors										
All-cause mortality	Unable to conduct sensitivity analysis as no data was imputed by authors										
Hospitalisation	Unable to conduct sensitivity analysis as no data was imputed by authors										
Revascularisation	Unable to conduct sensitivity analysis as no data was imputed by authors										
General HRQoL	Unable to conduct sensitivity analysis as no data was imputed by authors										
Cardiac-specific HRQoL [a]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single RCT where data was imputed by authors										
Stent thrombosis	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
MI [a]	Unable to conduct sensitivity analysis as no data was imputed by authors										
Stroke [a]	Unable to conduct sensitivity analysis as no data was imputed by authors										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no data was imputed by authors										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										

Abbreviations:

CABG: coronary artery bypass; **CI**: confidence interval; **HF:** heart failure; **HRQoL:** health-related quality of life; **MACE:** major adverse cardiac events; **MD:** mean difference; **MI:** myocardial infarction; **OMT:** optimal medical therapy; **SD:** standard deviation; **TVR:** target vessel revascularisation; **RCT**: randomised controlled trial; **RR**: risk ratio.

Notes:

[a] Original meta-analysis only included data from a single RCT.

OMT assumed to be equivalent between trial arms.

MACE defined as all-cause mortality, MI, stroke and/or hospitalisation.

Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

Table 89 Results of sensitivity analyses for PCI plus OMT compared to OMT alone (RCT)

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Risk of bias due to selection bias											
MACE	No difference from the analysis reported in ***Section 7.4.1.2***										
All-cause mortality	No difference from the analysis reported in ***Section 7.4.3.2***										
Hospitalisation [a]	No difference from the analysis reported in ***Section 7.4.6.2***										
Revascularisation	No difference from the analysis reported in ***Section 7.4.7.2***										
General HRQoL [a]	No difference from the analysis reported in ***Section 7.4.9.2***										
Cardiac-specific HRQoL	No difference from the analyses reported in ***Sections 7.4.11.1.2 to 7.4.11.5.2***										
Stent thrombosis	No difference from the analysis reported in ***Section 7.4.13.2***										
MI	No difference from the analysis reported in ***Section 7.4.15.2***										
Stroke	No difference from the analysis reported in ***Section 7.4.17.2***										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Risk of bias due to publications bias											
MACE	No difference from the analysis reported in ***Section 7.4.1.2***										
All-cause mortality	No difference from the analysis reported in ***Section 7.4.3.2***										
Hospitalisation [a]	No difference from the analysis reported in ***Section 7.4.6.2***										
Revascularisation	No difference from the analysis reported in ***Section 7.4.7.2***										
General HRQoL [a]	No difference from the analysis reported in ***Section 7.4.9.2***										

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Cardiac-specific HRQoL	No difference from the analyses reported in ***Sections 7.4.11.1.2 to 7.4.11.5.2***										
Stent thrombosis	No difference from the analysis reported in ***Section 7.4.13.2***										
MI	No difference from the analysis reported in ***Section 7.4.15.2***										
Stroke	No difference from the analysis reported in ***Section 7.4.17.2***										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Risk of bias due to missing outcomes											
MACE	No difference from the analysis reported in ***Section 7.4.1.2***										
All-cause mortality	No difference from the analysis reported in ***Section 7.4.3.2***										
Hospitalisation [a]	No difference from the analysis reported in ***Section 7.4.6.2***										
Revascularisation	No difference from the analysis reported in ***Section 7.4.7.2***										
General HRQoL [a]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single RCT that posed a high risk of bias										
Cardiac-specific HRQoL [b]	12 mo	SAQ	***AF***	***PCI + OMT***	***15.20 (29.00)***	***NA***	***44***	***NA***	***1.70***	***(-9.56, 12.96)***	***NA***
				OMT	***13.50 (25.00)***	***NA***	***45***	***NA***			
			AS	PCI + OMT	-2.80 (32.00)	NA	44	NA	-3.30	(-16.60, 10.00)	NA
				OMT	0.50 (32.00)	NA	45	NA			
			PL	***PCI + OMT***	***11.60 (24.00)***	***NA***	***44***	**NA**	**8.70**	**(-0.49, 17.89)**	**NA**
				OMT	***2.90 (20.00)***	***NA***	***45***	**NA**			
			QoL	***PCI + OMT***	***18.50 (24.00)***	***NA***	***44***	***NA***	***5.60***	***(-4.37, 15.57)***	***NA***
				OMT	***12.90 (24.00)***	***NA***	***45***	***NA***			

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
			TS	PCI + OMT	0.90 (17.00)	NA	44	NA	3.20	(-3.66, 10.06)	NA
				OMT	-2.30 (16.00)	NA	45	NA			
Stent thrombosis	No difference from the analysis reported in ***Section 7.4.13.2***										
MI	No difference from the analysis reported in ***Section 7.4.15.2***										
Stroke	No difference from the analysis reported in ***Section 7.4.17.2***										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Imputed data											
MACE	Unable to conduct sensitivity analysis as no data was imputed by authors										
All-cause mortality	Unable to conduct sensitivity analysis as no data was imputed by authors										
Hospitalisation [a]	Unable to conduct sensitivity analysis as no data was imputed by authors										
Revascularisation	Unable to conduct sensitivity analysis as no data was imputed by authors										
General HRQoL [a]	Unable to conduct sensitivity analysis as no data was imputed by authors										
Cardiac-specific HRQoL	12 mo	SAQ	***AF***	***PCI + OMT***	***15.20 (29.00)***	***NA***	***44***	***NA***	***1.70***	***(-9.56, 12.96)***	***NA***
				OMT	***13.50 (25.00)***	***NA***	***45***	***NA***			
			AS	PCI + OMT	-2.80 (32.00)	NA	44	NA	-3.30	(-16.60, 10.00)	NA
				OMT	0.50 (32.00)	NA	45	NA			
			PL	***PCI + OMT***	***11.60 (24.00)***	***NA***	***44***	***NA***	***8.70***	***(-0.49, 17.89)***	***NA***
				OMT	***2.90 (20.00)***	***NA***	***45***	***NA***			
			QoL	***PCI + OMT***	***18.50 (24.00)***	***NA***	***44***	***NA***	***5.60***	***(-4.37, 15.57)***	***NA***
				OMT	***12.90 (24.00)***	***NA***	***45***	***NA***			

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
			TS	PCI + OMT	0.90 (17.00)	NA	44	NA	3.20	(-3.66, 10.06)	NA
				OMT	-2.30 (16.00)	NA	45	NA			
Stent thrombosis	Unable to conduct sensitivity analysis as no data was imputed by authors										
MI	Unable to conduct sensitivity analysis as no data was imputed by authors										
Stroke	Unable to conduct sensitivity analysis as no data was imputed by authors										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										

Abbreviations:

AF: angina frequency; **AS:** anginal stability; **CI**: confidence interval; **HF:** heart failure; **HRQoL:** health-related quality of life; **MACE:** major adverse cardiac events; **MD:** mean difference; **MI:** myocardial infarction; **mo:** months; **NA:** not applicable; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **PL:** physical limitation; **QoL:** quality of life; **SAQ**: Seattle angina questionnaire; **SD:** standard deviation; **TS:** treatment satisfaction; **TVR:** target vessel revascularisation; **RCT**: randomised controlled trial; **RR**: risk ratio.

Notes:

[a] Original meta-analysis only included data from a single RCT.

OMT assumed to be equivalent between trial arms.

MACE was defined as all-cause mortality, MI, stroke and/or hospitalisation.

Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

Table 90 Results of sensitivity analyses for revascularisation plus OMT compared to OMT alone (RCT)

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Risk of bias due to missing outcomes											
MACE	No difference from the analysis reported in ***Section 7.4.1.3***										
All-cause mortality	No difference from the analysis reported in ***Section 7.4.3.3***										
Hospitalisation	No difference from the analysis reported in ***Section 7.4.5.3***										
Revascularisation	No difference from the analysis reported in ***Section 7.4.7.3***										
General HRQoL	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Cardiac-specific HRQoL	No difference from the analysis reported in ***Section 7.4.11.1.3 to 7.4.11.5.3***										
Stent thrombosis	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
MI	No difference from the analysis reported in ***Section 7.4.15.3***										
Stroke	No difference from the analysis reported in ***Section 7.4.17.3***										
Hospitalisation due to HF	No difference from the analysis reported in ***Section 7.4.19.3***										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Risk of bias due to publications bias											
MACE	No difference from the analysis reported in ***Section 7.4.1.3***										
All-cause mortality	No difference from the analysis reported in ***Section 7.4.3.3***										
Hospitalisation	No difference from the analysis reported in ***Section 7.4.5.3***										
Revascularisation	No difference from the analysis reported in ***Section 7.4.7.3***										
General HRQoL	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Cardiac-specific HRQoL	No difference from the analysis reported in ***Section 7.4.11.1.3 to 7.4.11.5.3***										
Stent thrombosis	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
MI	No difference from the analysis reported in ***Section 7.4.15.3***										
Stroke	No difference from the analysis reported in ***Section 7.4.17.3***										
Hospitalisation due to HF	No difference from the analysis reported in ***Section 7.4.19.3***										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Risk of bias due to selection bias											
MACE	No difference from the analysis reported in ***Section 7.4.1.3***										
All-cause mortality	No difference from the analysis reported in ***Section 7.4.3.3***										
Hospitalisation	No difference from the analysis reported in ***Section 7.4.5.3***										
Revascularisation	No difference from the analysis reported in ***Section 7.4.7.3***										
General HRQoL	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as the original meta-analysis only included a single RCT that posed a high risk of bias										
Stent thrombosis	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
MI	No difference from the analysis reported in ***Section 7.4.15.3***										
Stroke	No difference from the analysis reported in ***Section 7.4.17.3***										
Hospitalisation due to HF	No difference from the analysis reported in ***Section 7.4.19.3***										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Imputed data											

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
MACE	Unable to conduct sensitivity analysis as no data was imputed by authors										
All-cause mortality	Unable to conduct sensitivity analysis as no data was imputed by authors										
Hospitalisation	Unable to conduct sensitivity analysis as no data was imputed by authors										
Revascularisation	Unable to conduct sensitivity analysis as no data was imputed by authors										
General HRQoL	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as the original meta-analysis only included a single RCT that posed a high risk of bias										
Stent thrombosis	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										
MI	Unable to conduct sensitivity analysis as no data was imputed by authors										
Stroke	Unable to conduct sensitivity analysis as no data was imputed by authors										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no data was imputed by authors										
TVR	Unable to conduct sensitivity analysis as no RCTs were included in the original analysis										

Abbreviations:

CABG: coronary artery bypass; **CI**: confidence interval; **HF:** heart failure; **HRQoL:** health-related quality of life; **MACE:** major adverse cardiac events; **MD:** mean difference; **MI:** myocardial infarction; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **SD:** standard deviation; **TVR:** target vessel revascularisation; **REV:** revascularisation; **RCT**: randomised controlled trial; **RR**: risk ratio.

Notes:

[a] Original meta-analysis only included data from a single RCT.

OMT assumed to be equivalent between trial arms.

MACE defined as all-cause mortality, MI, stroke and/or hospitalisation.

Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

Table 91 Results of sensitivity analyses for CABG plus OMT compared to OMT alone (NRSI)

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Risk of bias due to selection bias [a]											
MACE	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
All-cause mortality [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Hospitalisation	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Revascularisation [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
MI [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Stroke	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Risk of bias due to publications bias [c]											
MACE	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
All-cause mortality [b]	Unable to conduct sensitivity analysis as the included NRSIs were retrospective and therefore bias cannot be appraised										
Hospitalisation	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Revascularisation [b]	Unable to conduct sensitivity analysis as the included NRSIs were retrospective and therefore bias cannot be appraised										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
MI [b]	Unable to conduct sensitivity analysis as the included NRSIs were retrospective and therefore bias cannot be appraised										
Stroke	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Risk of bias due to missing outcomes [d]											
MACE	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
All-cause mortality [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Hospitalisation	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Revascularisation [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
MI [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Stroke	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Imputed data											

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
MACE	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
All-cause mortality [b]	Unable to conduct sensitivity analysis as no data was imputed by authors										
Hospitalisation	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Revascularisation [b]	Unable to conduct sensitivity analysis as no data was imputed by authors										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
MI [b]	Unable to conduct sensitivity analysis as no data was imputed by authors										
Stroke	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										

Abbreviations:

CI: confidence interval; **HF:** heart failure; **HRQoL:** health-related quality of life; **MACE:** major adverse cardiac events; **MD:** mean difference; **MI:** myocardial infarction; **NRSI:** nonrandomised studies of interventions; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **SD:** standard deviation; **TVR:** target vessel revascularisation; **RR**: risk ratio.

Notes:

[a] Risk of bias caused by selection data was determined by combining statements 1.2 and 1.3 of an adapted version of the *Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort*.

[b] Original meta-analysis only included data from a single NRSI.

[c] Risk of bias caused by selective reporting was determined by statement 1.5 of an adapted version of the *Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort*.

[d] Risk of bias caused by missing data was determined by combining statements 1.7 and 1.9 of an adapted version of the *Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort*.

OMT assumed to be equivalent between trial arms.

MACE was defined as all-cause mortality, MI, stroke and/or hospitalisation.

Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

Table 92 Results of sensitivity analyses for PCI plus OMT compared to OMT alone (NRSI)

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Risk of bias due to missing outcomes [a]											
MACE	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate risk of bias										
All-cause mortality	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate risk of bias										
Hospitalisation	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate risk of bias										
Revascularisation	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate risk of bias										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
MI	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate risk of bias										
Stroke [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Risk of bias due to publications bias [c]											
MACE	No difference from the analysis reported in ***Section 7.4.2.2***										
All-cause mortality	No difference from the analysis reported in ***Section 7.4.4.2***										
Hospitalisation	Unable to conduct sensitivity analysis as the included NRSIs were retrospective and therefore bias cannot be appraised										
Revascularisation	No difference from the analysis reported in ***Section 7.4.8.2***										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis [b]	No difference from the analysis reported in ***Section 7.4.14.2***										
MI	Unable to conduct sensitivity analysis as the included NRSIs were retrospective and therefore bias cannot be appraised										
Stroke [b]	Unable to conduct sensitivity analysis as the included NRSIs were retrospective and therefore bias cannot be appraised										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR [b]	No difference from the analysis reported in ***Section 7.4.22.2***										
Risk of bias due to selection bias [d]											
MACE	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate to high risk of bias										
All-cause mortality	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate to high risk of bias										
Hospitalisation	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate risk of bias										
Revascularisation	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate to high risk of bias										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a high risk of bias										
MI	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate risk of bias										
Stroke [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a high risk of bias										
Imputed data											

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
MACE	Unable to conduct sensitivity analysis as no data was imputed by authors										
All-cause mortality	Unable to conduct sensitivity analysis as no data was imputed by authors										
Hospitalisation	Unable to conduct sensitivity analysis as no data was imputed by authors										
Revascularisation	Unable to conduct sensitivity analysis as no data was imputed by authors										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis [b]	Unable to conduct sensitivity analysis as no data was imputed by authors										
MI	Unable to conduct sensitivity analysis as no data was imputed by authors										
Stroke [b]	Unable to conduct sensitivity analysis as no data was imputed by authors										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR [b]	Unable to conduct sensitivity analysis as no data was imputed by authors										

Abbreviations:

CABG: coronary artery bypass; **CI**: confidence interval; **HF:** heart failure; **HRQoL:** health-related quality of life; **MACE:** major adverse cardiac events; **MD:** mean difference; **MI:** myocardial infarction; **OMT:** optimal medical therapy; **SD:** standard deviation; **TVR:** target vessel revascularisation; **RCT**: randomised controlled trial; **RR**: risk ratio.

Notes:

[a] Risk of bias caused by selection data was determined by combining statements 1.2 and 1.3 of an adapted version of the *Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort*.

[b] Original meta-analysis only included data from a single NRSI.

[c] Risk of bias caused by selective reporting was determined by statement 1.5 of an adapted version of the *Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort*.

[d] Risk of bias caused by missing data was determined by combining statements 1.7 and 1.9 of an adapted version of the *Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort*.

OMT assumed to be equivalent between trial arms.

MACE was defined as all-cause mortality, MI, stroke and/or hospitalisation.

Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

Table 93 Results of sensitivity analyses for revascularisation plus OMT compared to OMT alone (NRSI)

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Risk of bias due to missing outcomes [a]											
MACE	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
All-cause mortality [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Hospitalisation [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Revascularisation	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate risk of bias										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
MI [b]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Stroke	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Risk of bias due to publications bias [c]											
MACE	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
All-cause mortality [a]	No difference from the analysis reported in ***Section 7.4.4.3***										
Hospitalisation [a]	Unable to conduct sensitivity analysis as the included NRSIs were retrospective and therefore bias cannot be appraised										
Revascularisation	No difference from the analysis reported in ***Section 7.4.8.3***										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
MI [a]	Unable to conduct sensitivity analysis as the included NRSIs were retrospective and therefore bias cannot be appraised										
Stroke	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Risk of bias due to selection bias [d]											
MACE	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
All-cause mortality [a]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a high risk of bias										
Hospitalisation [a]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Revascularisation	Unable to conduct sensitivity analysis as the original meta-analysis included NRSIs that posed a moderate to high risk of bias										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
MI [a]	Unable to conduct sensitivity analysis as the original meta-analysis only included a single NRSI that posed a moderate risk of bias										
Stroke	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Imputed data											

Outcome	Timepoint	Tool	Domain	Treatment	Mean (SD)	Event	Sample size	Effect size		95% CI	Heterogeneity (I^2)
								RR	MD		
MACE	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
All-cause mortality [a]	Unable to conduct sensitivity analysis as no data was imputed by authors										
Hospitalisation [a]	Unable to conduct sensitivity analysis as no data was imputed by authors										
Revascularisation	Unable to conduct sensitivity analysis as no data was imputed by authors										
General HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Cardiac-specific HRQoL	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Stent thrombosis	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
MI [a]	Unable to conduct sensitivity analysis as no data was imputed by authors										
Stroke	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
Hospitalisation due to HF	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										
TVR	Unable to conduct sensitivity analysis as no NRSIs were included in the original analysis										

Abbreviations:

CABG: coronary artery bypass; **CI**: confidence interval; **HF:** heart failure; **HRQoL:** health-related quality of life; **MACE:** major adverse cardiac events; **MD:** mean difference; **MI:** myocardial infarction; **OMT:** optimal medical therapy; **PCI:** percutaneous coronary intervention; **SD:** standard deviation; **TVR:** target vessel revascularisation; **REV:** revascularisation; **NRSI:** nonrandomised studies of interventions; **RR**: risk ratio.

Notes:

[a] Risk of bias caused by selection data was determined by combining statements 1.2 and 1.3 of an adapted version of the *Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort*.

[b] Original meta-analysis only included data from a single NRSI.

[c] Risk of bias caused by selective reporting was determined by statement 1.5 of an adapted version of the *Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort*.

[d] Risk of bias caused by missing data was determined by combining statements 1.7 and 1.9 of an adapted version of the *Scottish Intercollegiate Guidelines Network (SIGN) Checklist for Cohort*.

OMT assumed to be equivalent between trial arms.

MACE defined as all-cause mortality, MI, stroke and/or hospitalisation.

Only hospitalisation for MI, stroke and/or heart failure was considered clinically relevant.

Revascularisation defined as a population where CABG or PCI were conducted; populations where CABG and PCI occurred concurrently were excluded.

18 Appendix E: Ongoing and recently completed clinical trials

Table 94 Ongoing clinical trials fitting the inclusion criteria

Trial registry ID; Country	Indications; Sample size (n)	Intervention	Comparator	Primary outcome(s)	Recruitment status; Start date; Expected completion date
ClinicalTrials.gov					
NCT03563417 Denmark	Chronic total occlusion in native coronary artery 1,560	PCI	OMT	MACE, HRQoL	Recruiting, Start date: November 6, 2018; Completion date: November 1, 2032
NCT03756870 Netherlands	Chronic total occlusion 82	PCI	OMT	Ischaemic burden assessed with exercise myocardial perfusion SPECT-CT, QoL left ventricular ejection fraction	Recruiting, Start date: July 1, 2019 Completion date: January 1, 2029
EU clinical trials register					
None found	NA	NA	NA	NA	NA
Australian New Zealand clinical trials registry					
None found	NA	NA	NA	NA	NA

Abbreviations:

HRQoL: Health-related Quality of Life; **MACE**: Major adverse cardiovascular events; **NA:** Not applicable **OMT**: Optimal Medical Therapy; **PCI**: Percutaneous Coronary Intervention.

19 Appendix F: Economic appendices

19.1 Economic evidence tables

Table 95 Economic evidence table: cost-effectiveness of CABG

Author, year	Perspective	Intervention, comparator	Population characteristics	Analysis methods	Source of evidence	Results	Additional comments
Chew, 2022	US healthcare system.	CABG + OMT vs OMT alone.	Patients ≥18 years of age with LVEF ≤35% and CAD amenable to CABG. Median age (years): 60 Female (%): 12 History of MI (%): 77 Diabetes (%): 39 NYHA class III or IV (%): 37 LVEF ≤28% (%): 54 3-vessel CAD (%): 36 Left main or proximal left anterior descending CAD (%): 69.	**Evaluation type**: model based. **Model type**: individual patient-level state transition simulation model with 2 health states (alive and dead). **Time horizon**: lifetime. **Discount rate**: 3% p.a. for costs and outcomes. **Cycle length**: 1 month.	STICH trial for: **All-cause mortality**: survival data from the trial and its extended follow-up (median follow-up: 9.8 years). **HRQoL**: EQ-5D-3L responses collected at 4, 12, 24 and 36 months according to randomised allocation (i.e. intention to treat). These were converted to preference-weighted health indices. **Medical resource use**: within trial resource use data (initial CABG procedure; hospitalisations, inpatient procedures, and hospital-based outpatient procedures). External cost weights were applied. Annual medication and outpatient medical care costs were estimated from external sources. They were assumed to be similar between arms.	**10-year ICER (cost per QALY):** US$120,288/QALY. 34% and 69% chance of meeting a US$100,000 and US$150,000 WTP threshold, respectively. **Lifetime ICER (cost per QALY):** US$63,989/QALY. 87% and 97% chance of meeting a US$100,000 and US$150,000 WTP threshold, respectively. **Subgroup analyses:** (1) LVEF ≤28%: $51,370/QALY vs LVEF>28%: $90,687/QALY (2) 0–2 vessel CAD: $106,752/QALY vs 3 vessel CAD: $41,476/QALY. **Key drivers:** Risk reduction in all-cause mortality beyond 2 years for CABG (vs OMT), Cardiac surgery costs in CABG arm, and Assumption re: extrapolation of utilities (sustained vs attenuated).	**The STICH trial:** The STICH trial was an RCT conducted across 22 countries. Participants were enrolled from 2002 to 2007 and follow-up extended until 2015. In total 1,212 patients were randomised, 610 to the CABG + OMT arm and 602 to OMT alone. **Author's conclusion:** In patients with ischaemic cardiomyopathy and a reduced LVEF, CABG is economically attractive relative to OMT alone at current WTP thresholds in the US.

Abbreviations:

CABG: coronary artery bypass graft; **CAD**: coronary artery disease; **EQ-5D-3L**: EuroQol 5-dimension – 3-level version; **HRQoL**: health-related quality of life; **ICER**: incremental cost-effectiveness ratio; **LVEF**: left ventricular ejection fraction; **MI**: myocardial infarction; **NYHA**: New York Heart Association; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **QALY**: quality-adjusted life year; **RCT**: randomised controlled trial; **STICH**: Surgical Treatment for Ischemic Heart Failure; **US**: United States; **WTP**: willingness-to-pay.

Table 96 Economic evidence table: cost-effectiveness of PCI

Author, year	Perspective	Intervention, comparator	Population characteristics	Analysis methods	Source of evidence	Results	Additional comments
Fearon, 2018	US healthcare system.	Second generation PCI-DES + OMT vs OMT.	Patients age ≥21 years with stable angina, single- or multi-vessel CAD, ≥1 stenosis in a major coronary artery with FFR ≤0.8 and LVEF ≥30%. FAME 2 (PCI; OMT)[108] Mean age (years): 64; 64 Male (%): 80; 77 History of MI (%): 37; 38 Diabetes (%): 28; 27 CCS class 0–I (%): 30; 33 CCS class II (%): 46; 45 CCS class III–IV (%): 24; 23 LVEF <50% (%): 20; 14 Single vessel (%): 56; 59.	**Evaluation type**: trial based. **Time horizon**: 3 years. **Discount rate**: none.	FAME 2 trial for: **QoL**: EQ-5D collected at baseline, 1 month, and 1, 2 and 3 years according to randomised allocation (i.e. intention to treat), and with multiple imputation for missing values. Weighted using US utility weights. **Survival:** within trial (3-year) survival data. **Resource use:** within trial resource use data. US cost weights applied.	**2-year ICER (cost per QALY):** US$17,300/QALY. **3-years (cost per QALY):** US$1,600/QALY. PCI-DES had an 85% chance of being below a WTP threshold of US$50,000. **Sensitivity analysis:** The ICER changed numerically in several sensitivity analyses (in which the cost of certain parameters was varied) but remained <US$50,000/QALY.	**The FAME 2 trial:** An RCT conducted across 28 sites in Europe and North America between May 2010 and January 2012.[108] In total, 888 patients were randomised, 447 to FFR-guided PCI and 441 to OMT alone. **Author's conclusion:** 3-year results from the FAME 2 trial show that, in patients with CCS and at least 1 lesion with an abnormal FFR, PCI improves outcomes and is economically attractive compared with OMT alone.

Author, year	Perspective	Intervention, comparator	Population characteristics	Analysis methods	Source of evidence	Results	Additional comments
Fearon, 2013	US healthcare system. NB: suggests societal, however only medical costs included.	Second generation PCI-DES + OMT vs OMT.	Patients age ≥21 years with stable angina, single- or multi-vessel CAD, ≥1 stenosis in a major coronary artery with FFR ≤0.8 and LVEF ≥30%. Characteristics according to the FAME 2 study cohort,[108] which are described above for Fearon, 2018.	**Type**: trial based. **Time horizon**: multiple used depending on assumption for extrapolation of HRQoL benefit (up to 4 years; 3 years in the base case). NB: Difference in cost at 12 months is assumed to remain constant over the extrapolation period. **Discount rate**: none.	FAME 2 trial for: **QoL**: EQ-5D collected at baseline, 1 month, and 12 months. Weighted using US utility weights. NB: only the baseline and 1 month data were used. Also, survival doesn't seem to have been considered. **Resource use:** within trial resource use data for index procedure, hospitalisation, and subsequent follow-up (up to 12 months). US cost weights applied.	**Base case ICER (cost per QALY):** US$36,000/QALY. PCI-DES has 80% and 99.5% chance of being cost effective at WTP thresholds of US$50,000 and US$100,000. **Subgroup analysis:** CCS 0–1: ICER of $102,000/QALY vs CCS 2–4: ICER of $26,000/QALY **Scenario analysis:** NB: list not comprehensive Assume effect of PCI dissipated over 2 or 4 years: $54,000/QALY and $27,000/QALY. 12 month time horizon with assumption OMT patients have increase in utility after revascularisation: $60,000/QALY	**Author's conclusion:** In patients with symptomatic CCS, PCI in the setting of an abnormal FFR improves angina and HRQoL and appears to be economically attractive compared with OMT if one assumes that the benefit of PCI lasts longer than 1 year.
Gada, 2012	US healthcare provider.	PCI vs OMT. NB: It is unclear if OMT was included in the intervention arm. Also, PCI-DES and PCI-BMS are not differentiated.	Patients with CTO, chronic stable angina, CCS class III–IV. Hypothetical model cohort has an initial start age of 60 years.	**Evaluation type**: model based. **Model type**: Markov model. Events/states: peri-procedural events (arterial complications, MI, tamponade, CABG, CVA, death); post-PCI states (successful or unsuccessful); post-PCI events (MI, TVR [PCI or CABG], stent thrombosis or death). Patients on OMT had annual rates of CABG and death. **Time horizon**: 5 years. **Discount rate**: 5% p.a. for costs and outcomes. **Cycle length**: 1 year.	**Utility**: EQ-5D utilities derived from SAQ scores from the FACTOR trial and other literature sources for disabling CVA and CABG. **Costs**: cost for the procedures from the authors' institution; follow-up costs from the literature. **Transition probabilities:** observational studies.	**5-year ICER (cost per QALY):** US$9,505/QALY. PCI had ~60% probability of being cost effective at a WTP threshold of US$50,000. **Key drivers:** The utility values of each of the major health states (i.e. the post-successful PCI, post-unsuccessful PCI, and OMT states) was the most important driver. Costs associated with OMT, and the rate of successful PCI were other important drivers. NB: the authors note that this finding (i.e. that HRQoL is a key driver of the cost-effectiveness of PCI) underscores the need to further assess utilities in patients who are candidates for PCI.	**Author's conclusion:** The results of this decision-analytic model suggest that CTO-PCI is cost effective in a patient population with severe symptoms.

Author, year	Perspective	Intervention, comparator	Population characteristics	Analysis methods	Source of evidence	Results	Additional comments
Gorenoi, 2011	German restricted societal. NB: suggests a restricted societal perspective, however only medical costs included.	PCI + OMT vs OMT. NB: PCI-DES in only 5% of the cohort.	Patients with stable angina.	**Evaluation type**: model based. **Model type:** simplified linear simulation model. **Time horizon**: 5 years. **Outcome**: incremental cost per patient with avoided AP attacks. NB: It was assumed that the cost difference was caused exclusively by a difference in the rate of revascularisation with PCI (primary and during follow-up).	**Costs**: German costing data for the cost of revascularisation (from German DRGs) and for clopidogrel. **Effect estimates**: accompanying systematic review and meta-analysis. The analysis included the BARI-2D, COURAGE and OAT trials.	**5-year ICER (cost per patient year free from angina):** €24,805 per patient year free from angina.	**Author's conclusion:** Although there are no recognised WTP values against which to assess the cost-effectiveness of an intervention in relation to avoided angina episodes, the authors conclude that PCI cannot be considered cost effective, citing a WTP of US$8,000 to avoid repeat revascularisation.[159]
Kodera, 2019 NB: Relevant for the angina cohort only.	Japanese healthcare system.	FFR-guided PCI vs OMT. NB: It is unclear if OMT was included in the intervention arm.	Patients with symptomatic angina and significant stenosis confirmed on FFR. Mean age (years): 67 Male (%): 70 CCS score ≥2 (%): 70 Diabetes (%): 36 Single-vessel CAD (%): 76	**Evaluation type**: model based. **Model type**: Markov model with 8 health states (AP, acute MI, old MI, new PCI, post PCI, new stroke, old stroke, and dead). **Time horizon**: 30 years. **Discount rate**: 2% p.a. for costs and outcomes. **Cycle length**: 1 month.	**CV event rates**: the FAME 2 study and the CREDO Kyoto Japanese registry-based study of PCI. **QoL:** EQ-5D data from the FAME 2 study, supplemented with literature-based values for the MI and stroke health states. **Resource use/costs:** literature-based cost estimates.	**30-year ICER (cost per QALY):** ¥4.63 million/QALY. 50.4% probability that PCI is cost effective at WTP threshold of ¥5 m. **Scenario analyses:** NB: list not comprehensive Asymptomatic without diabetes: ¥23.0m Asymptomatic with diabetes: ¥7.02m No CVD event reduction with PCI: ¥26.2 m 2-fold HRQoL increase with PCI: ¥1.98 m QoL increase for PCI last 2 years: ¥24.1 m 5-year time horizon: ¥14.5 m 10-year time horizon: ¥8.66 m.	**Author's conclusion**: FFR-guided PCI for symptomatic angina could be cost effective compared with OMT alone.

Author, year	Perspective	Intervention, comparator	Population characteristics	Analysis methods	Source of evidence	Results	Additional comments
Wijeysundera, 2013	Canadian third-party healthcare payer.	(1) PCI-DES + OMT and (2) PCI-BMS + OMT vs OMT.	Patients with CCS with symptoms sufficient to warrant coronary angiography and with angiographic confirmation of hemodynamically significant coronary stenoses. Theoretical cohort: mean age (years): 63 Male (%): 71 CCS class 0–I (%): 14 CCS class II (%): 22 CCS class III–IV (%): 65.	**Evaluation type**: model based. **Model type**: Markov model with 4 subtrees: (1) OMT only; (2) PCI; (3) MI; (4) CABG (if need for revascularisation after 3 previous PCIs only). **Time horizon**: lifetime. **Discount rate**: 5% p.a. for costs and outcomes. **Cycle length**: 1 month.	**Transition probabilities:** for PCI-BMS and PCI-DES: the Ontario Cardiac Care Network PCI registry up to 3 years & literature beyond 3 years. For medical therapy: literature. **Utilities:** literature based. **Resource use:** medication use from COURAGE trial with Ontario Drug Benefit Formulary unit costs. For clinical events (PCI, CABG, hospitalisation for MI), unit costs from the Ontario Case Costing Initiative.	NB: ICERs for PCI-DES vs OMT have been calculated manually, as the original publication included PCI-BMS in efficiency frontier calculations. **Lifetime ICER (PCI-DES vs OMT; cost per QALY):** ~ Canadian $25,840/QALY **Subgroup analyses (PCI-DES vs OMT):** Non-diabetic, short lesion, large artery: $19,009 Non-diabetic, long lesion, small artery: $39,660 Diabetic, short lesion, large artery: $28,155 Diabetic, short lesion, small artery: $20,209 Diabetic, long lesion, large artery: $8,583 Diabetic, long lesion, small artery: $18,245	**Author's conclusion:** This evaluation of PCI vs OMT found that an initial strategy of PCI-BMS was cost-effective. NB: Estimates for DES were predominantly from first generation stents. Also, the calculated pairwise ICER suggests PCI-DES may also be cost effective relative to OMT at the WTP threshold of Canadian $50,000 per QALY.

Abbreviations:

AP: angina pectoris; **BARI-2D:** Bypass Angioplasty Revascularization Investigation 2 Diabetes; **CAD**: coronary artery disease; **CCS:** Canadian Cardiovascular Society; **COURAGE**: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; **CREDO**: Coronary Revascularization Demonstrating Outcome; **CTO**: chronic total occlusion; **CV:** cardiovascular; **CVA:** cerebrovascular accident; **DRG**: diagnosis-related group; **EQ-5D**: EuroQol 5-dimension FACTOR**:** FlowCardia's Approach to Chronic Total Occlusion Recanalisation; **FAME:** Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; **FFR**: fractional flow reserve; **HRQoL**: health-related quality of life; **ICER**: incremental cost-effectiveness ratio; **MI**: myocardial infarction; **NHS**: National Health Service; **LV**: left ventricular; **NA**: not applicable; **OAT:** Occluded Artery Trial; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **PCI-BMS**: percutaneous coronary intervention with bare metal stent(s); **PCI-DES**: percutaneous coronary intervention with drug eluting stent(s); **QALY:** quality adjusted life year; **SAQ**: Seattle Angina Questionnaire; **RCT**: randomised controlled trial; **TVR**: target vessel revascularisation; **US**: United States.

Table 97 Economic evidence table: costing studies

Author, year	Perspective	Intervention, comparator	Population characteristics	Analysis methods	Source of evidence	Results	Additional comments
Caruba, 2015	French healthcare payer.	CABG + OMT, PCI-DES + OMT, PCI-BMS + OMT and OMT alone.	Hypothetical model cohort (n=1,000). The cohort comprised male and female patients 50–70 years of age with CCS (i.e. no acute coronary syndrome or MI in the last 24 hours).	**Evaluation type**: Modelling study. **Modelling details**: for each treatment strategy, costs were estimated for 6 clinical scenarios: clinical success; recurrence of symptoms without hospitalisation or revascularisation; MI; subsequent revascularisation without MI; death from non-cardiac cause; cardiac death. These costs were multiplied by the probability of each clinical scenario under each strategy to derive total cost per patient. **Time horizon**: 1 year.	**Resource use:** determined from guidelines and clinical studies or, in the absence of information, from expert opinion. **Treatment effect:** the probabilities of a patient being in each of the 6 clinical scenarios after 1 year, according to the initial treatment used, were derived via a literature search. If the required probabilities could not be derived from the literature, they were informed by expert opinion.	**1-year cost per patient; mean (95% CI):** OMT: €1,567 (95% CI: 1,421 to 1,713) PCI-BMS: €5,908 (5,699 to 6,118) PCI-DES: €6,623 (6,409 to 6,839) CABG: €16,612 (16,218 to 17,005).	**Author's conclusion:** OMT appears to be the least costly option over 1 year. If reasonable from a clinical point of view, OMT might achieve appreciable savings in health expenditures compared with invasive treatments.

Author, year	Perspective	Intervention, comparator	Population characteristics	Analysis methods	Source of evidence	Results	Additional comments
Kang, 2016	Canadian third-party healthcare payer.	CABG, PCI and OMT alone. NB: We have assumed that OMT is provided in all treatment groups..	Patients who underwent angiography for the indication of CCS (Oct 2008–Sept 2011) and who had obstructive coronary stenosis. OMT: n=15,138; revascularisation: n=23,988 (PCI: n=15,601; CABG: n=8,387). <u>Analysis cohort (OMT; revascularisation):</u> Mean age (years): 67; 65 Male (%): 74; 76 History of MI (%): 36; 23 Diabetes (%): 48; 41 History of smoking (%): 33; 31 LVEF ≤34% (%): 8; 4 LVEF 34-49% (%): 16; 11 LVEF ≥50% (%): 47; 50 CCS class 0–I (%): 38; 26 CCS class II (%): 36; 40 CCS class III–IV (%): 27; 34	**Evaluation type:** retrospective observational study. **Time horizon:** 1 year. **Discount rate:** none used. NB: the primary outcome was the total cumulative cost per patient in the 1 year following the index angiography. Complete cost profiles were available for all patients for 1 year or until death. NB: patients with PCI or CABG within 90 days of the index angiogram were assigned to the revascularisation group. All other patients were assigned to the OMT group.	Administrative databases in Ontario, Canada. Specifically, data from the Cardiac Care Network of Ontario was linked with population-level administrative databases.	**1-year costs revascularisation vs OMT:** Acute care hospital admission: Canadian$14,109 vs $7,038, p<0.001 ED: $375 vs $367, p=0.3 Surgery: $3,071 vs $2,090, p<0.001 Physician visits: $6,313 vs $4,079, p<0.001 Medication (patients age >65 years only): $1,780 vs $1,857, p=0.004 Laboratory: $193 vs $195, p=0.3 Long-term care: $29 vs $93, p<0.001. Most healthcare costs were due to acute care hospital admission, with a significantly higher cost for patients undergoing revascularisation than for patients receiving OMT. Revascularisation was a significant predictor of mean cost regardless of the modality (PCI: cost ratio 1.27, 95% CI: 1.24–1.31; CABG: cost ratio 2.62, 95% CI 2.53–2.71).	**Cardiac Care Network of Ontario:** Network of 19 hospitals that provide adult cardiac services. It includes a registry of patients who undergo cardiac angiography, PCI or CABG. **Author's conclusion:** In this study, the major driver for 1-year costs was revascularisation. The decision to pursue a revascularisation strategy has a substantial impact on healthcare resources. The use of a short time horizon may bias results against CABG, because it is associated with fewer revascularisations in the long term.

Author, year	Perspective	Intervention, comparator	Population characteristics	Analysis methods	Source of evidence	Results	Additional comments
McCreanor, 2019	Australian healthcare payer (limited to drug costs).	CABG + OMT, PCI + OMT and OMT alone.	Patients with CAD (for OMT group, self-reported; for PCI or CABG group; with history of a relevant MBS procedure). OMT: n=609; PCI: n=92; CABG: n=39. <u>Analysis cohort (OMT; PCI; CABG):</u> Mean age (years): 62; 62; 63 Female (%): 16; 17; 8 Current smoker (%): 5; 9; 5 Past smoker (%): 48; 50; 44 Diabetic (%): 7; 9; 8.	**Evaluation type:** observational study using administrative data. **Time horizon:** 1 year. NB: the analysis cohort was selected from the broader QSkin study cohort. Participants who underwent PCI or CABG were identified using MBS codes. For the OMT group, patients who self-reported a history of CAD, had private health insurance and were taking ≥2 different types of CAD drugs were selected.	**Resource use:** PBS data for PBS-listed pharmaceuticals used in the treatment of CAD were extracted for 1 full year. Relevant drugs included: antiplatelets (aspirin, clopidogrel, prasugrel, ticagrelor); lipid modifiers (fibrates, statins); antianginal drugs for symptom relief (beta blockers, CCBs, nitrates, renin angiotensin system antagonists, other). These data were used to calculate an annual cost per patient.	**Average annual pharmaceutical costs (mean; 95% CI):** OMT: AUD$1,481 (95% CI: $1,416 to $1,546) PCI: AUD$1,920 ($1,752 to $2,089) CABG: AUD$881 ($739 to $1,023). **Duration of DAPT (median; range)** OMT (n=141): 31 months (1–40) PCI (n=49): 16 months (1–40).	**QSkin study cohort** The QSkin study cohort comprised ~40,000 people age 40–69 from Queensland, Australia. Recruitment was between Nov 2010 and Dec 2011 with follow-up through to June 2014. **Author's conclusion:** A common argument for PCI in CCS is that it reduces the burden of medical therapy, particularly the need for symptom relief medications. However, this study found that PCI did not affect the costs or use of drugs used for angina relief. Further, the study showed that DAPT may frequently be continued for longer than recommended by the guidelines.

Author, year	Perspective	Intervention, comparator	Population characteristics	Analysis methods	Source of evidence	Results	Additional comments
Stenvall, 2017	Finnish secondary healthcare provider (drug costs not included).	CABG, PCI and OMT alone. NB: We have assumed that OMT is provided in all treatment groups.	Stable patients entering elective coronary angiography (Nov 2002–Mar 2003) in whom CAD was confirmed. OMT: n=105; PCI =94; CABG: n=101. Analysis cohort (OMT; PCI; CABG): Mean age (years): 65; 61; 65 Male (%): 67; 73; 85 Previous MI (%): 35; 34; 42 Diabetic (%): 31; 20; 34 Current or ex-smoker (%): 61; 64; 58 NHYA class III (%): 26; 37; 54 NYHA class IV (%): 0; 4; 2 LVEF ≤50% (%): 24; 13; 35 LMCA (%): 0; 0; 19 3-vessel CAD (%): 22; 18; 57.	**Evaluation type:** prospective observational study. **Time horizon:** 8 years. **Discount rate:** none used. NB: The costs are at current prices for each actual year without adjusting for inflation.	Data concerning costs and utilisation of secondary care services during the years 2002–2011 for 296 patients living in the immediate catchment area of the hospital were obtained from the administrative database of the hospital.	**Secondary care costs over 8-year period:** OMT: Mean (SD): €4,514 (14,244) Median (range): €1,770 (677 to 143,170) PCI: Mean (SD): €7,245 (5,649) Median (range): €5,548 (915 to 31,954) CABG Mean (SD): €17,498 (14,518) Median (range): €13,560 (8,306 to 141,256). NB: the difference between groups reduced slightly when standardised for the baseline characteristics; however, the difference remained statistically significant. Mean costs after standardisation: OMT: €4,580; PCI: €6,920; CABG: €16,730.	NB: In this study, patients with complex CAD (i.e. LMCA and multi-vessel disease) were most commonly treated by CABG, according to contemporary guidelines. **Author's conclusion:** The 8-year mean secondary care costs of CABG were over 2-fold and almost 4-fold higher than PCI + OMT, respectively, even after adjustment for baseline characteristics.

Abbreviations:
AUD: Australian dollar; **CABG**: coronary artery bypass graft; **CAD**: coronary artery disease; **CCB:** calcium channel blocker; **CCS**: Canadian Cardiovascular Society; **CI**: confidence interval; **CI**: confidence interval; **DAPT**: dual antiplatelet therapy; **ED**: emergency department; **LMCA**: left main coronary artery; **LVEF**: left ventricular ejection fraction; **MBS**: Medicare Benefits Schedule; **MI**: myocardial infarction; **NB**: note before; **NYHA**: New York Heart Association; **OMT**: optimal medical therapy; **PBS**: Pharmaceutical Benefits Scheme; **PCI**: percutaneous coronary intervention; **PCI-BMS**: percutaneous coronary intervention with bare metal stent(s); **PCI-DES**: percutaneous coronary intervention with drug eluting stent(s); **SD**: standard deviation.

19.2 Applicability of the economic evidence

Table 98 Assessment of applicability: cost-effectiveness analyses

	1.1 Is the study population appropriate for the review question?	*1.2 Are the interventions appropriate for the review question?*	*1.3 Is the system in which the study was conducted sufficiently similar to the current Swiss context?*	*1.4 Is the perspective for costs appropriate for the review question?*	*1.5 Is the perspective for outcomes appropriate for the review question?*	*1.6 Are all future costs and outcomes discounted appropriately?*	*1.7 Are QALYs or an appropriate social care-related equivalent used as an outcome?*	*Overall Judgement*
Chew, 2022	Partly. Patients with LVEF ≤35%.	Partly. Study enrolment 2002–2007; surgical techniques could be outdated.	Partly. United States	Yes	Yes	Yes	Yes	*Partially applicable.*
Fearon, 2018	Partly. Patients with ≥1 stenosis with FFR ≤0.8.	Partly. Second generation DES.	Partly. United States	Yes	Yes	No	Yes	*Partially applicable.*
Fearon, 2013	Partly. Patients with ≥1 stenosis with FFR ≤0.8.	Partly. Second generation DES.	Partly. United States	Yes	Yes	No	Yes	*Partially applicable.*
Gada, 2012	Partly. Restricted to patients with CTO.	Partly. Combines BMS and DES. Unclear if OMT included in intervention.	Partly. United States	Yes	Yes	Yes	Yes	*Not applicable.*
Gorenoi, 2011	Yes	Partly. Combines BMS and DES; heavily weighted toward BMS (only 5% DES).	Partly. German	Yes	Yes	No	No. Cost per avoided angina episode.	*Not applicable.*
Kodera, 2019	Partly. Patients with ≥1 stenosis with FFR ≤0.8.	Partly. Unclear if OMT included in intervention arm.	Partly. Japanese	Yes	Yes	Yes	Yes	*Not applicable.*
Wijeysundera, 2013	Yes	Partly. Both BMS and DES included. DES mostly first generation.	Partly. Canadian.	Yes	Yes	Yes	Yes	*Not applicable.*

Abbreviations:
BMS: bare-metal stent; **DES**: drug-eluting stent; **FFR:** fractional flow reserve; **LVEF**: left ventricular ejection fraction; **OMT**: optimal medical therapy; **QALY**: quality-adjusted life year
Notes:
Directly applicable studies = meet all applicability criteria or, if not, the unmet criteria are unlikely to change the conclusions about cost-effectiveness. Partially applicable studies = failed to meet one or more criteria and this could change the conclusions about cost-effectiveness. Not applicable studies = failed to meet one or more criteria and this was likely to change the conclusions about cost-effectiveness.

19.3 List of included ICD-10-GM and CHOP codes

Table 99 List of ICD-10-GM codes considered for the budget impact analysis

ICD-10-GM code	Description
I20.1	Angina pectoris with proven coronary spasm
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I25.0	Atherosclerotic cardiovascular disease, so described
I25.10	Atherosclerotic heart disease: without hemodynamically effective stenoses
I25.11	Atherosclerotic heart disease: single-vessel disease
I25.12	Atherosclerotic heart disease: 2-vessel disease
I25.13	Atherosclerotic heart disease: 3-vessel disease
I25.14	Atherosclerotic heart disease: left main stem stenosis
I25.15	Atherosclerotic heart disease: with stenosed bypass vessels
I25.16	Atherosclerotic heart disease: with stenosed stents
I25.19	Atherosclerotic heart disease: unspecified
I25.4	Coronary artery aneurysm
I25.5	Ischemic cardiomyopathy
I25.6	Silent myocardial ischemia
I25.8	Other forms of chronic ischemic heart disease

Abbreviations:
ICD-10-GM: International Classification of Disease – 10th revision – German Modification.

Table 100 List of CHOP codes considered for the budget impact analysis

CHOP code	Description
PCI	
36.07.10	Delivery of drug-eluting coronary artery stent(s), bioresorbable stent(s)
36.07.11	Delivery of drug-eluting, self-expanding coronary artery stent(s)
36.07.99	Delivery of drug-eluting coronary artery stent(s), others
00.66.29	Coronary angioplasty (PTCA), with balloons, other
00.66.21	Coronary angioplasty (PTCA) with drug-eluting balloons
00.4C.12	Insertion of 2 drug-eluting balloons
CABG	
36.11.21	Simple (aorto)coronary bypass, open surgery (thoracotomy, mini-thoracotomy, sternotomy), with autogenous artery, A. radialis
36.11.22	Simple (aorto)coronary bypass, open surgery (thoracotomy, mini-thoracotomy, sternotomy), with autogenous artery, internal mammary artery (internal thoracic artery)
36.11.23	Simple (aorto)coronary bypass, open surgical (thoracotomy, mini-thoracotomy, sternotomy), with autogenous artery, free internal mammary artery (internal thoracic artery) transplant (IMA transplant)
36.11.26	Simple (aorto)coronary bypass, open surgery (thoracotomy, mini-thoracotomy, sternotomy), with autogenous vein, without external stabilization mesh)
36.11.27	Simple (aorto)coronary bypass, open surgery (thoracotomy, mini-thoracotomy, sternotomy), with autogenous vein, with external stabilization mesh
36.11.32	Simple (aorto)coronary bypass, minimally invasive, with autogenous artery, internal mammary artery (internal thoracic artery)

CHOP code	Description
36.11.36	Simple (aorto)coronary bypass, minimally invasive, with autogenous vein, without external stabilization mesh
36.12.21	Double (aorto)coronary bypass, open surgical (thoracotomy, mini-thoracotomy, sternotomy), with autogenous artery, A. radialis
36.12.22	Double (aorto)coronary bypass, open surgical (thoracotomy, mini-thoracotomy, sternotomy), with autogenous artery, internal mammary artery (internal thoracic artery)
36.12.23	Double (aorto)coronary bypass, open surgical (thoracotomy, mini-thoracotomy, sternotomy), with autogenous artery, free internal mammary artery (internal thoracic artery) transplant
36.12.26	Double (aorto)coronary bypass, open surgical (thoracotomy, mini-thoracotomy, sternotomy), with autogenous vein, without external stabilization mesh
36.12.27	Double (aorto)coronary bypass, open surgical (thoracotomy, mini-thoracotomy, sternotomy), with autogenous vein, with external stabilization mesh
36.13.22	Triple (aorto)coronary bypass, open surgical (thoracotomy, mini-thoracotomy, sternotomy), with autogenous artery, internal mammary artery (internal thoracic artery)
36.13.23	Triple (aorto)coronary bypass, open surgical (thoracotomy, mini-thoracotomy, sternotomy), with autogenous artery, free internal mammary artery (internal thoracic artery) transplant
36.13.26	Triple (aorto)coronary bypass, open surgery (thoracotomy, mini-thoracotomy, sternotomy), with autogenous vein, without external stabilization mesh
36.18.12	Quadruple (aorto)coronary bypass, open surgical (thoracotomy, mini-thoracotomy, sternotomy), with autogenous artery, internal mammary artery (internal thoracic artery)
36.18.16	Quadruple (aorto)coronary bypass, open surgery (thoracotomy, mini-thoracotomy, sternotomy), with autogenous vein, without external stabilization mesh
36.1A.12	Fivefold (aorto)coronary bypass, open surgical (thoracotomy, mini-thoracotomy, sternotomy), with autogenous artery, internal mammary artery (internal thoracic artery)
36.1A.16	Fivefold (aorto)coronary bypass, open surgery (thoracotomy, mini-thoracotomy, sternotomy), with autogenous vein, without external stabilization mesh
36.1C.11	Simple (aorto)coronary bypass
36.1C.12	Double (aorto)coronary bypass
36.1C.13	Triple (aorto)coronary bypass
36.1C.14	Quadruple (aorto)coronary bypass
36.1C.15	Fivefold (aorto)coronary bypass
36.1C.16	Sixfold and multiple (aorto)coronary bypass
36.1D.11	Off-pump coronary artery bypass (beating heart surgery)
36.1D.12	Minimally invasive direct coronary artery bypass) (surgery on the beating heart)

Abbreviations:

CABG: coronary artery bypass graft; **CHOP:** Swiss classification of surgical interventions; **PCI**: percutaneous coronary intervention; **PTCA**: percutaneous transluminal coronary angioplasty.

19.4 SAQ to EQ-5D mapping algorithm

The algorithm used in the model to map SAQ component scores to an EQ-5D utility score is shown below:[179]

$$EQ - 5D = \beta_0 + \beta_1 AF + \beta_2 AS + \beta_3 DP + \beta_4 PL + \beta_5 TS$$

Abbreviations:
AF: angina frequency; **AS**: angina stability; **DP**: disease perception (or quality of life); **EQ-5D**: Euro-QoL 5 dimensions; **PL**: physical limitations; **TS**: treatment satisfaction.

With the following parameter values:[179]

- β_0: 0.4388 (0.4015 to 0.4763)
- β_1: 0.0010 (0.0007 to 0.0013)
- β_2: –0.0002 (–0.0005 to 0)
- β_3: 0.0023 (0.002 to 0.0027)
- β_4: 0.0019 (0.0017 to 0.0022)
- β_5: 0.0004 (–0.0001 to 0.0008)

19.5 Summary of economic model assumptions

Key structural assumptions underpinning the economic evaluation are summarised in ***Table 101***.

Table 101 List of key structural assumptions

Assumption	Comment
Annual cycle length	An annual cycle allowed for a return transition from the MI or REV states to the well-with-CCS state 1 year after the event. Patients considered to have CCS if they have not had an acute event in the past 12 months.[1]
Additional costs and HRQoL reductions after an acute event are incurred for 1 year. After a year, patients return to the well-with-CCS state.	12 months after an ACS event, patients would be classified as having CCS;[1] therefore, fit within the well-with-CCS definition. Nevertheless, this is a limitation of the analysis as the full benefit of avoided MACE events may not be captured.
All patients in the well-with-CCS state are at the same risk of future events, regardless of whether they have experienced a prior event.	Per the Markovian assumption,[193] the model has no memory of what has occurred in earlier model cycles. Memory states were not incorporated. This is a limitation of the analysis.
Results were analysed in a stepped fashion using length of longest follow-up and lifetime time horizons.	Beyond trial follow, extrapolations are required which introduce uncertainty into the analysis. Nevertheless, a lifetime horizon was needed to capture in full the differences between intervention and comparator.
For patients receiving OMT alone, risks of all MACE events apart from all-cause mortality (for which age-based adjustments are incorporated) are constant over time.	Assumption.
For patients receiving an invasive intervention, the benefits (if any) on event risks and HRQoL were assumed to attenuate after the period of longest follow-up.	Assumption. For the effect of PCI on HRQoL, this assumption was tested in scenario analysis.

Assumption	Comment
For patients receiving an invasive intervention, constant transition probabilities for all MACE events (apart from all-cause mortality) were applied during the follow-up period.	Assumption.
Following either PCI or MI, patients receive DAPT for 6 to 12 months Note: 9 months was used in calculations.	According to ESC guidelines, 12 months is the recommended default duration of DAPT after ACS, but shorter durations may be considered in patients with a high bleeding risk.[1] After PCI for stable angina, the guidelines suggest 6 months of DAPT achieves the optimal balance of efficacy and safety in most patients.[1]
There would be a reduction in the use of antianginal medications in the 5 or 10 years after PCI and REV or CABG, respectively.	Expert advice patients on OMT after REV would require less antianginal medication. In practice, a cost analysis found that PCI did not affect the cost or use of drugs for angina relief.[135] Nevertheless, in RCTs, a reduction in use of antianginal medications has been observed.[12,116,117]

Abbreviations:

ACS: acute coronary syndrome; **CABG**: coronary artery bypass graft; **CCS**: chronic coronary syndrome; **DAPT**: dual antiplatelet therapy; **HRQoL**: health-related quality of life; **MACE**: major adverse cardiac event; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **REV**: revascularisation.

19.6 Summary tables of the economic model inputs

Table 102 Summary table for the cost and cost-related model inputs

Description of the parameter	Mean	Lower	Upper	Standard error of the mean	Distribution	Notes; source
Cost inputs (CHF)						
Inpatient PCI, unit cost	12,216.93	8,061.00	30,712.80	3,054.23	Gamma	Swiss DRG version 11.0[162]
Outpatient PCI, unit cost	2,510.36	1,841.51	3,922.38	627.59	Gamma	TARMED; 2022 Swiss cantonal tax points.[160]
CABG, unit cost	40,459.52	35,301.20	51,886.60	10,114.88	Gamma	Swiss DRG version 11.0[162]
MI event cost	8,786.64	6,927.00	17,728.15	2,196.66	Gamma	
Stroke event cost	12,432.44	3,363.44	46,224.25	3,108.11	Gamma	
Hospitalisation for HF event cost	10,907.10	9,321.05	25,297.25	2,726.77	Gamma	
Annual cost for aspirin	60.40					Spezialitätenliste[164]
Annual cost for clopidogrel	375.95					
Annual cost for betablockers [A]	284.15					
Annual cost for CCB [B]	172.79					
Annual cost antianginal medication [C]	421.74					
Annual cost of follow up in the year after revascularisation or MI	418.60					Assumed to comprise 2 GP visits, 2 ECGs, and 1 echocardiogram in 50% of patients based on ESC guidelines.[1] TARMED; 2022 Swiss cantonal tax points.[160]
Annual cost of follow up, ongoing	248.56					Assumed to comprise 1 GP visit, 1 ECG, a biannual blood test and an echocardiogram every 4 years based on ESC guidelines.[1] TARMED; Analysenliste; 2022 Swiss cantonal tax points.[160]
Cost-related inputs						

Description of the parameter	Mean	Lower	Upper	Standard error of the mean	Distribution	Notes; source
Proportion of PCIs that are outpatient	0.224	0.2	0.3	0.0224	Beta	Assumed proportion of PCIs performed in an outpatient (vs inpatient) setting.
Proportion of revascularisation procedures that are PCI	0.740	0.6	0.9	0.074	Beta	Assumed proportion of revascularisation procedures that are PCI (vs CABG). Applied to the revascularisation (any) intervention and all subsequent revascularisations. Based on initial procedures performed among patients in the invasive intervention arm of ISCHEMIA.[12]
Baseline proportion of patients on aspirin	0.951					Baseline utilisation based upon data from the western/central European patients in the CLARIFY registry.[155]
Baseline proportion of patients on DAPT [D]	0.253					
Baseline proportion of patients on betablocker therapy	0.77					
Baseline proportion of patients on CCB	0.262					
Baseline proportion of patients taking antianginal medication	0.252					
Relative use of antianginal medications after revascularisation (vs. OMT alone)	0.50	0	1	0.2551	Beta	Arbitrary assumption 50% (0-100%) patients initially using antianginal medications would require them in the 5 years (10 years for CABG) after revascularisation.
Proportion patients receiving DAPT after PCI or MI	1.00	0.5	1			Assumption that 100% (50-100%) patients would require DAPT after PCI or MI.

Abbreviations:
CABG: coronary artery bypass graft; **CCB**: calcium channel blocker; **CHF**: Swiss francs; **DAPT**: dual antiplatelet therapy; **ECG**: electrocardiogram; **GP**: general practitioner; **HF**: heart failure; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention.

Table 103 Summary table for the health state utility-related model inputs

Description of the parameter	Mean	Lower	Upper	Standard error of the mean	Distribution	Notes; source
Mapping algorithm coefficients						
Constant (ß0) of the algorithm	0.4388	0.4015	0.4763	0.0191	Normal	Algorithm used to map SAQ component scores to an EQ-5D utility score. Published by Wijeysundera et al. (2014)[179]
AF regression coefficient (ß1)	0.0010	0.0007	0.0013	0.0002	Normal	
AS regression coefficient (ß2)	-0.0002	-0.0005	0	0.0001	Normal	
DP/QoL regression coefficient (ß3)	0.0023	0.002	0.0027	0.0002	Normal	
PL regression coefficient (ß4)	0.0019	0.0017	0.0022	0.0001	Normal	
TS regression coefficient (ß5)	0.0004	-0.0001	0.0008	0.0002	Normal	
Baseline (OMT alone) SAQ component scores						
AF component score	79.3	77.53	81.07	0.9031	Normal	Baseline SAQ component scores based on a cohort of 660 Austrian patients with stable angina.[181]
AS component score	65.5	63.47	67.53	1.0354	Normal	
DP/QoL component score	63.7	61.85	65.55	0.9420	Normal	
PL component score	67.5	65.64	69.36	0.9498	Normal	
TS component score	86.3	85.06	87.54	0.6306	Normal	
Treatment effect of revascularisation + OMT (mean difference vs OMT alone)						
Difference in AF component score at 12 months	1.80	0.41	3.19	0.709	Normal	Meta-analyses performed for this HTA (see ***Figure 33***, ***Figure 37*** and ***Figure 39***, ***Section 7.4***)
Difference in AF component score at 24 months	1.45	-0.11	3.01	0.796	Normal	
Difference in AF component score at 60 months	0.82	-1.02	2.66	0.939	Normal	
Difference in DP/QoL component score at 12 months	3.56	1.65	5.47	0.974	Normal	
Difference in DP/QoL component score at 24 months	1.97	-0.09	4.03	1.051	Normal	
Difference in DP/QoL component score at 60 months	0.47	-2.17	3.11	1.347	Normal	
Difference in PL component score at 12 months	1.25	-0.72	3.22	1.005	Normal	
Difference in PL component score at 24 months	1.57	-0.74	3.88	1.179	Normal	

Description of the parameter	Mean	Lower	Upper	Standard error of the mean	Distribution	Notes; source
Difference in PL component score at 60 months	0.18	-3.00	3.36	1.622	Normal	
Difference in TS component score at 12 months	1.97	0.66	3.28	0.668	Normal	
Difference in TS component score at 24 months	1.71	0.3	3.12	0.719	Normal	
Difference in TS component score at 60 months	0.26	-1.59	2.11	0.944	Normal	
Treatment effect of PCI + OMT (mean difference vs OMT alone)						
Difference in AF component score at 12 months	3.94	0.29	7.59	1.862	Normal	Meta-analyses performed for this HTA (see ***Figure 32***, ***Figure 34***, ***Figure 36***, ***Figure 38*** and ***Figure 40***, ***Section 7.4***)
Difference in AS component score at 12 months	1.04	-3.1	5.17	2.110	Normal	
Difference in DP/QoL component score at 12 months	4.98	0.25	9.71	2.413	Normal	
Difference in PL component score at 12 months	4.79	0.35	9.22	2.263	Normal	
Difference in TS component score at 12 months	1.22	-1.64	4.07	1.457	Normal	
Treatment effect of CABG + OMT (mean difference vs OMT alone)						
Difference in AF component score at 12 months	6.60	4.05	9.15	1.301	Normal	Meta-analyses performed for this HTA (see ***Figure 31*** and ***Figure 35***, ***Section 7.4***)
Difference in AF component at 24 months	4.00	1.45	6.55	1.301	Normal	
Difference in AF component score at 60 months	1.30	-1.29	3.89	1.321	Normal	
Difference in DP/QoL component score at 12 months	6.70	3.76	9.64	1.500	Normal	
Difference in DP/QoL component at 24 months	6.80	3.59	10.01	1.638	Normal	
Difference in DP/QoL component score at 60 months	2.40	-0.74	5.54	1.602	Normal	
Event-related health state utilities						
Health state utility in the year after MI	0.67	0.623	0.716	0.024	Beta	Health state utilities in the year following an acute event, as valued by general population participants in the UK using the time trade-off method.[182]
Health state utility in the year after stroke	0.33	0.267	0.396	0.033	Beta	
Health state utility in the year after an HF event	0.60	0.546	0.653	0.027	Beta	
Health state utility in the year after subsequent revascularisation	0.67	0.623	0.716	0.024	Beta	

Abbreviations:

AF: angina frequency; **AS**: angina stability; **CABG**: coronary artery bypass graft; **DP**: disease perception; **EQ-5D**: European quality of life 5-dimension questionnaire; **HF**: heart failure; **HTA**: health technology assessment; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **PL**: physical limitations; **QoL**: quality of life; **SAQ**: Seattle Angina Questionnaire; **TS**: treatment satisfaction; **UK**: United Kingdom.

Table 104 Summary table of the baseline annual transition probabilities (i.e. probabilities for OMT alone)

Description of the parameter	Mean	Lower	Upper	Standard error of the mean	Distribution	Notes; source
Baseline (i.e. for patients on OMT alone) annual transition probabilities						
Any state to death (all causes)	0.0172	0.0103	0.0256	0.004	Beta	5-year cumulative event probabilities from ISCHEMIA.[12] Converted to annual transition probabilities in 2-steps:[171] • 5-year probability converted to an annual rate • Annual rate converted to annual probability.
Well with CCS to MI (non-fatal)	0.0232	0.0129	0.0362	0.006	Beta	
Well with CCS to stroke (non-fatal)	0.0037	0.0020	0.0059	0.001	Beta	
Well with CCS to subsequent revascularisation	0.0396	0.0225	0.0614	0.010	Beta	
Well with CCS to HF hospitalisation	0.0032	0.0015	0.0055	0.001	Beta	
Baseline (i.e. for patients on OMT alone) annual transition probabilities for the high event risk based on FFR (i.e. FFR <0.8) subgroup; PCI only						
Any state to death (all causes)	0.0106	0.00553	0.01743	0.003	Beta	5-year cumulative event probabilities from FAME 2.[118] Converted to annual transition probabilities in 2-steps:[171] • 5-year probability converted to an annual rate • Annual rate converted to annual probability.
Well with CCS to MI (non-fatal)	0.0234	0.01307	0.03662	0.006	Beta	
Well with CCS to stroke (non-fatal)	0.0025	0.00095	0.00476	0.001	Beta	
Well with CCS to subsequent revascularisation	0.0828	0.0466	0.12805	0.021	Beta	
Well with CCS to HF hospitalisation	0.0032	0.00152	0.00548	0.001	Beta	Assumed equivalent to the annual transition probability used in the base case (i.e. derived from ISCHEMIA 5-year cumulative probability).[12]
Baseline (i.e. for patients on OMT alone) annual transition probabilities for the LVEF <35% subgroup; CABG only						
Any state to death (all causes)	0.1025	0.05695	0.15978	0.026	Beta	10-year cumulative event probabilities (5-year for revascularisation) from STICH.[116]
Well with CCS to MI (non-fatal)	0.0088	0.00528	0.01306	0.002	Beta	

Description of the parameter	Mean	Lower	Upper	Standard error of the mean	Distribution	Notes; source
Well with CCS to stroke (non-fatal)	0.0054	0.00362	0.00755	0.001	Beta	Converted to annual transition probabilities in 2-steps:[171] • 10-year probability (or 5-year for revascularisation) converted to an annual rate • Annual rate converted to annual probability.
Well with CCS to subsequent revascularisation	0.0357	0.02024	0.05528	0.009	Beta	
Well with CCS to HF hospitalisation	0.0393	0.02217	0.06132	0.010	Beta	
Baseline (i.e. for patients on OMT alone) annual transition probabilities for the CKD subgroup						
Any state to death (all causes)	0.1029	0.0822	0.1254	0.0110	Beta	3-year cumulative event probabilities from ISCHEMIA-CKD.[104] Converted to annual transition probabilities in 2-steps:[171] • 3-year probability converted to an annual rate • Annual rate converted to annual probability.
Well with CCS to MI (non-fatal)	0.0520	0.0390	0.0672	0.0072	Beta	
Well with CCS to stroke (non-fatal)	0.0041	0.0015	0.0091	0.0019	Beta	
Well with CCS to subsequent revascularisation	0.0385	0.0214	0.0604	0.010	Beta	
Well with CCS to HF hospitalisation	0.0121	0.0064	0.0208	0.0037	Beta	

Abbreviations:

CABG: coronary artery bypass graft; **CCS**: chronic coronary syndrome; **CKD**: chronic kidney disease; **FFR**: fractional flow reserve; **HF**: heart failure; **LVEF**: left ventricular ejection fraction; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention.

Table 105 Summary table for treatment effect-related model inputs

Description of the parameter	Mean	Lower	Upper	Mean of logs [A]	Standard error of logs [A]	Distribution	Notes; source
Revascularisation + OMT vs OMT alone							
RR for all-cause mortality, 60 months	0.93	0.85	1.02	-0.0726	0.0465	Lognormal	***Figure 11***
RR for MI, 60 months	0.88	0.77	1	-0.1278	0.0667	Lognormal	***Figure 46***
RR for stroke, 60 months	1.42	0.76	2.64	0.3507	0.3177	Lognormal	***Figure 52***
RR for subsequent revascularisation, 60 months	0.54	0.47	0.62	-0.6162	0.0707	Lognormal	***Figure 24***
RR for HF hospitalisation, 60 months	1.83	1.23	2.73	0.6043	0.2034	Lognormal	***Figure 55***
PCI + OMT vs OMT alone							
RR for all-cause mortality, 60 months	1.13	0.86	1.49	0.1222	0.1402	Lognormal	***Figure 10***

Description of the parameter	Mean	Lower	Upper	Mean of logs [A]	Standard error of logs [A]	Distribution	Notes; source
RR for MI, 60 months	0.67	0.45	1.00	-0.4005	0.2037	Lognormal	***Figure 45***
RR for stroke, 60 months	1.69	0.67	4.26	0.5247	0.4719	Lognormal	***Figure 51***
RR for subsequent revascularisation, 60 months	0.43	0.17	1.1	-0.8440	0.4763	Lognormal	***Figure 23***
RR for HF hospitalisation, 60 months	1	NA	NA	NA	NA	Lognormal	Due to an absence of data, it was assumed that PCI plus OMT has no differential effect relative to OMT alone on HF hospitalisations.
CABG + OMT vs OMT alone							
RR for all-cause mortality, 120 months	0.89	0.82	0.97	-0.1165	0.0429	Lognormal	***Figure 9***
RR for MI, 120 months	0.66	0.44	0.99	-0.4155	0.2069	Lognormal	***Figure 44***
RR for stroke, 120 months	1.13	0.76	1.69	0.1222	0.2039	Lognormal	***Figure 50***
RR for subsequent revascularisation, 60 months	0.33	0.12	0.89	-1.1087	0.5112	Lognormal	***Figure 22***
RR for HF hospitalisation, 120 months	0.77	0.65	0.92	-0.2614	0.0886	Lognormal	***Figure 54***

Abbreviations:

CABG: coronary artery bypass graft; **HF**: heart failure; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **RR**: risk ratio.

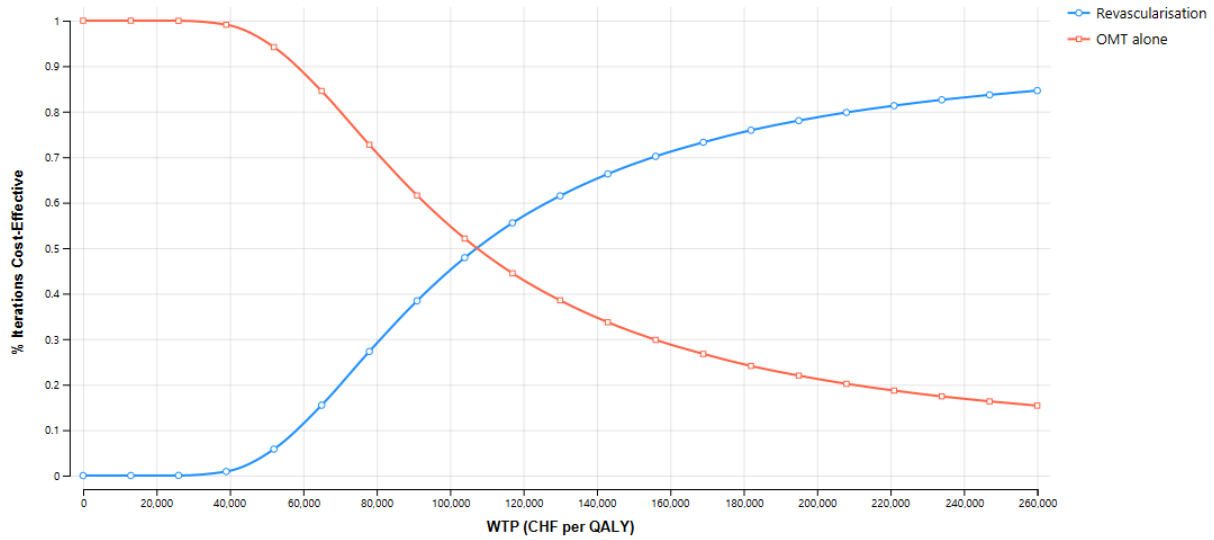
Notes:

A: Lognormal distributions were used; therefore, mean of log and standard error of logs are presented.

19.7 Cost-effectiveness acceptability curves for scenario analyses

19.7.1 Revascularisation plus OMT in patients with chronic kidney disease

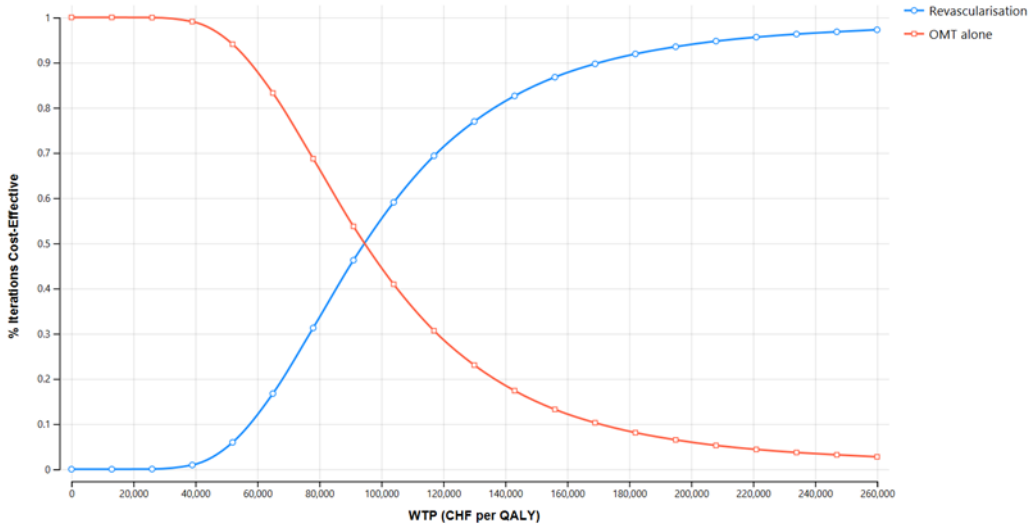
Figure 68 Cost-effectiveness acceptability curve for scenario analysis on revascularisation plus OMT



Abbreviations:
CHF: Swiss franc; **OMT**: optimal medical therapy; **QALY**: quality adjusted life year; **REV**: revascularisation; **WTP**: willingness-to-pay.

19.7.2 CABG plus OMT vs OMT alone in patients with reduced LVEF

Figure 69 Cost-effectiveness acceptability curve for scenario analysis on CABG plus OMT



Abbreviations:
CABG: coronary artery bypass graft; **CHF**: Swiss franc; **LVEF**: left ventricular ejection fraction; **OMT**: optimal medical therapy; **QALY**: quality adjusted life year; **WTP**: willingness-to-pay.