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Health Technology Assessment (HTA)

HTA Protocol

Title	Revascularisation versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)
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Technology	Percutaneous transluminal coronary intervention (coronary angioplasty) Coronary artery bypass grafting (CABG) Optimal medical therapy (OMT)
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Executive Summary

Patients with chronic coronary syndrome (CCS) may be treated with optimal medical therapy (OMT), percutaneous coronary intervention (PCI) with OMT, or coronary artery bypass grafting (CABG) with OMT. These interventions are publicly reimbursed in Switzerland, and their use is well established in patients with acute coronary syndrome (i.e. those experiencing myocardial infarction or unstable angina). However, the comparative safety and effectiveness of PCI with OMT and CABG with OMT compared to OMT alone in CCS patients is unclear. The Federal Office of Public Health has contracted an independent evaluation of PCI and CABG in the population of CCS patients.

A systematic review of five databases (PubMed [MEDLINE], EMBASE [Ovid], the Cochrane Library, the INAHTA database and Econlit) will be conducted to capture contemporary literature. Medications and surgical techniques for the treatment of CCS are rapidly evolving technologies. Therefore, only studies from the year 2010 onwards will be considered. Due to the highly patient-specific and complex nature of OMT, OMT will not be defined in the study inclusion criteria. Recent systematic reviews (SRs) and meta-analyses (MA) that answer the research questions will be considered. Randomised controlled trials (RCTs) will be included in the absence of, or to update, existing SRs and MAs. Adverse event data may be supplemented with non-RCT data. If appropriate, the primary data will undergo a longitudinal meta-analysis. In the absence of long-term data, a pairwise meta-analysis will be performed to demonstrate the comparative clinical effectiveness of the interventions in CCS patients. Subgrouping, sensitivity analyses, and meta-regression will be performed to investigate variables among the data.

A secondary systematic search will identify literature that addresses the economic research questions. An independent evaluation will be performed in the absence of existing economic studies relevant to Swiss practice. This approach, refined through the HTA process, will most likely be evaluated through a Markov cohort model with a cost-utility analysis. Current cost and utility data from Switzerland will serve as inputs for the model. A budget impact analysis will be performed.

Social, legal, ethical, and organisational issues will be addressed through non-systematic, targeted searches. Issues highlighted in studies within the clinical section will also be included. The findings will be summarised narratively.

Contents

Tables

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 Francs
CI	Confidence interval
CMR	Cardiac magnetic resonance imaging
COPD	Chronic obstructive pulmonary disease
CTA	Coronary computerised tomography angiography
CTO	Chronic coronary total occlusion
CUA	Cost-utility analysis
CVD	Cardiovascular disease
DALYs	Disability-Adjusted Life Years
DEB	Drug-eluting balloon
DES	Drug-eluting stent
DHP-CCB	Dihydropyridine calcium channel blockers
DRG	Diagnosis-related groups
ECG	Electrocardiogram
EKG	Echocardiogram
EQ-5D	European quality of life five dimension
ESC	European Society of Cardiology
GRADE	Grading of Recommendation, Assessment, Development and Evaluations
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICA	Invasive coronary angiography
ICHOM	International Consortium for Health Outcomes Measurement
ICTRP	International clinical trials registry platforms
IMA	Internal mammary/thoracic artery
INAHTA	Internal Network of Agencies for Health Technology Assessments
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
mmol/L	Millimoles per litre
NRSI	Non-randomised study of interventions
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin-kexin type 9

PICO	Population, intervention, comparator, outcome
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
SD	Standard deviation
SF-36	Short form-36
SMD	Standardised mean differences
SoF	Summary of findings
VKA	Vitamin K antagonist
WHO	World Health Organization

Objective of the HTA Protocol

Based on a preliminary screening of the literature, the objectives of the health technology assessment (HTA) protocol are to:

- formulate the research question
- define the population, intervention, comparator, outcomes (PICO)
- describe the methodology to conduct a systematic literature search, extract, analyse and synthesise the data, and present the result in an HTA report on the topic.

Key questions are defined, addressing the main HTA domains – efficacy/effectiveness/safety, costs/budget impact/cost-effectiveness, ethical/legal/social issues and organisational issues.

1 Policy question

Each HTA topic entails a policy and a research question. In health care, 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) and risk factor modifications (e.g. 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 percutaneous transluminal coronary angioplasty – or coronary artery bypass grafting (CABG).[1] These interventions aim to improve quality of life 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]

To evaluate the available evidence regarding efficacy, effectiveness, and safety of PCI with OMT and CABG with OMT compared to OMT alone, an HTA will be conducted. The proposed HTA will also involve an economic evaluation of the intervention and comparator. Additionally, ethical, legal, social and organisational issues are to be explored.

An HTA will be of considerable value in determining whether the costs and benefits of invasive coronary artery surgery (i.e. PCI and CABG) justify the coverage of these services by mandatory health insurance for patients with CCS.

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 impact 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, or organisational issues associated with PCI plus OMT or 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 the disease include ischemia, 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 can be controlled through pharmaceutical intervention or revascularisation procedures.[1,15] In addition, advanced calcification that causes 100% occlusion of a coronary artery for over three months (chronic total occlusion [CTO]), is considered to be an exacerbation of CCS.[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] Atrial atherosclerotic lesions are at risk of plaque rupture, during which the coagulation cascade (thrombogenesis) is set in motion and leads to constriction or occlusion of the vascular lumen.[19] This may lead to myocardial infarction and/or 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 this artery narrowing, known as stenosis, is not necessarily dependant on the 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] Heart failure, left ventricular remodelling, myocardial ischaemia or necrosis, and ischaemic cardiomyopathy result from restricted blood flow caused by arterial stenoses.[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 pectoria), shortness of breath, nausea, faintness, restlessness, a sense of impending doom, or chest discomfort.[1,14,17,20] The 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 the arms, wrists, or fingers.[1,21] These symptoms may be brought on 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 goals when treating CCS are 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 is an extensive process that generally involves physical examination, family history, 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 in high-risk patients where the type of revascularisation (i.e. PCI or CABG) that needs to be undertaken can only be determined with detailed visualisation.[1] The types of invasive and non-invasive diagnostic testing recommended by the *European Society of Cardiology (ESC)* guidelines are detailed.[1]

Non-invasive testing

- **Biochemical tests:** laboratory investigations are performed to identify cardiovascular risk factors (e.g. high cholesterol, diabetes mellitus [type 1 or 2], renal dysfunction, etc.), and disease prognosis. Common tests include haemoglobin A1c (HbA1c), lipid profile (e.g. total cholesterol, high density cholesterol, triglycerides, and low-density lipoprotein cholesterol [LDL-C]), troponin T or I (for myocardial injury), and glomerular filtration rate (GFR).[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]
- **Echocardiogram (EKG) – resting or stress**: details cardiac structure, function, and anatomy using sound waves.[17] Resting EKGs are a clinical tool that aid in the identification of regional wall motion abnormalities (indication of CCS) and diastolic functions, and the exclusion of other causes of ischemia and/or angina. In addition, resting EKGs can also aid in the diagnosis of concurrent cardiac diseases (e.g. heart failure, valvular diseases, cardiomyopathies). Stress EKG can be used to detect MI through exercise or pharmacological induced wall motion abnormalities.[1,17]

- **Cardiac magnetic resonance (CMR) imaging** – **resting or stress**: details cardiac anatomy and function, when EKGs are inconclusive.[17] Resting CMR can evaluate both regional and global cardiac function. The imaging can also evaluate systolic cardiac function and cardiac anatomy. Late gadolinium enhancement of CMR 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] The tests do not provide information that is directly important to CCS diagnosis. The information provided is helpful detecting potential heart failure and/ or pulmonary conditions. The main use of chest X-rays is to exclude additional causes of atypical presentation of chest pain**.**[1]
- **Coronary computerised tomography angiography (CTA):** uses ionising radiation (X-ray imaging) to visualise the heart and the lumen of surrounding arteries.[25] CTA provides detailed non-invasive anatomical visualisation that is able to detect obstructive stenoses.[1,25]

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 generally only indicated for patients suspected of having CCS if non-invasive testing is inconclusive. In some circumstances, ICA may be indicated if a non-invasive testing indicates a patient has a high risk of a cardiac event and the type of revascularisation (i.e. PCI or CABG) needs to be determined.[1]

3.3 Epidemiology and burden of disease

The term cardiovascular disease (CVD) represents a group of diseases that affect the heart and blood vessels (e.g. CCS, heart failure, etc.).[26-28] CVD is a leading cause of death in Switzerland and globally.[26,27] In 2019, CVD was the number one cause of death in Switzerland, responsible for 29% of all deaths.[26] 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.[26] In 2015, there were 19,501 reported new cases of CCS in Swiss males, and 15,370 new cases in women.[29] Switzerland has one of the lowest rates of age-standardised disease adjusted life years (DALYs) lost in males due to stroke, ischaemic heart disease and other CVDs.[29] Furthermore, in 2018 a Swiss cohort of CCS patients reported a 0.2% mortality rate after PCI.[30]

Statistics from the United States of America report that 38% of all deaths are attributable to CVD, and of these 47% were patients with CCS.[31] In 2015, CCS accounted for approximately 14% of deaths in men and 12% in women in Europe;[29] European men with CCS lost more than 21 million DALYs (14%); European women lost around 14.5 million (11.3%) DALYs.[29]

3.4 Treatment pathway

The treatment for CCS can depend on a variety of risk factors, including comorbidities (e.g. hypertension, diabetes mellitus (type 1 and 2), obesity, hyperlipidaemia, chronic kidney disease), diet, smoking status, exercise regimen, and if the patient is symptomatic or asymptomatic.[1,20,23,32] In general, the first step in a treatment pathway is to determine if the patient is symptomatic or asymptomatic. If the symptoms are reducing the patient's quality of life and/or the disease state and progression places the patient at an increased risk of an acute event (e.g. myocardial infarction [MI], heart failure, cardiovascular death, etc.), then the patient is indicated for further testing and angiogram with subsequent revascularisation (PCI or CABG), if necessary. When the symptoms do not affect the patient's quality of life and/or disease state, and progression do not place the patient at an increased risk of an acute event, the patient will be indicated for OMT alone. If the patient is tolerating OMT and does not develop symptoms and/or the disease does not progress, the patient will continue with their CCS management under their treating physician. In contrast, if the patient is not tolerating OMT or the disease does progress, the patient will likely be indicated for invasive coronary intervention.

A patient's synergy between percutaneous coronary intervention with taxus and cardiac surgery II (SYNTAX II) score and/or additional diagnostic information (***Section 3.2***) may be used to determine if they are indicated for PCI or a CABG procedure.[33] This tool was developed with the SYNTAX II Trial, incorporating the anatomical presentation of the disease to determine complexity and risk of CCS.[33] After invasive surgery, patients are generally treated with OMT (if the patient can tolerate OMT). If the patient's symptoms have not been relieved and/or the disease continues to progress after surgical intervention, the patient can undergo a subsequent invasive coronary intervention (PCI or CABG). If the patient's symptoms have been relieved and/or the disease does not progress after undergoing an invasive coronary procedure, the patient will continue to have their CCS managed by their treating physician.

4 Technology description

Invasive and non-invasive treatments are available for the treatment of symptomatic CCS patients.[1] There are several modifications of each therapy to suit individual patient needs. The 2019 ESC guidelines highlight three primary goals of treatment in CCS:[1]

- improve health-related quality of life (via reducing frequency and severity of angina pectoris and other somatic and psychological complaints)
- reduce CCS-related morbidity (non-fatal MI and heart failure)
- 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), left ventricular ejection fraction (LVEF), presence of multivessel disease, presence of main stem stenosis, and the SYNTAX II score – determine if a patient is indicated for PCI (also commonly known as angioplasty or percutaneous transluminal coronary angioplasty [PTCA]) or CABG.[34]

Some patients may have to undergo subsequent invasive revascularisation procedures.[35,36] Compared to PCI-naïve patients, patients that have had a prior PCI are at an increased risk of having to undergo CABG within 6 months.[36] Similarly, patients that underwent PCI within 6 months of their original PCI are twice as likely to have an additional PCI compared to naïve patients.[36] However, compared to naïve patients, patients that had a prior CABG are less likely to have to undergo an additional CABG procedure.[36]

4.1.1 Percutaneous coronary intervention

PCI is a minimally invasive approach, in which stenoses are directly manipulated to restore patency of the vessels and blood flow to the affected myocardial area. This may be performed with the placement of a bare-metal stent (BMS), drug-eluting stent (DES), or via balloon angioplasty.[37-39]

The individual procedures are described as follows:

- **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.[37,39] Afterwards, the device is retracted and removed.[37,39] Balloon angioplasty was first used to treat CCS in 1977.[38,39] 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).[40,41] However, in this procedure the balloons are used to deliver a homogenous coating of immediate release, high concentration, short-acting pharmaceuticals (i.e. antiproliferative agents) to the surface of lesions.[40,42] DEBs are designed to compress the plaque while concurrently eluting pharmaceuticals that prevent restenosis of the artery.[40-42] Unlike DESs and BMSs, DEBs can be utilised in torturous (i.e. long complex, twisted) vessels, small vessels, and calcified vessels.[40]
- **Bare-metal stent angioplasty:** Like balloon angioplasty, a catheter feeds a stent to the stenosis. The stent is placed and retained to mechanically sustain the opening of the artery and stabilise plaque.[37] This method may be most appropriate for patients with intolerances to the drugs associated with DES.[43] A BMS was first implanted into human coronary artery in 1986.[39] In 2018, 0.2% of stents implanted Switzerland were BMS.[30]
- **Drug-eluting stent (DES) angioplasty:** DES are the most common stent choice in angioplasty.[30] These stents act similarly to BMS; however, they are also coated with medications to prevent restenosis through neointimal hyperplasia.[37] Three generations of DESs have been released and used since the first implantation of such a medical device in 1999.[38,39] In 2018, 99% of the stent type implanted in Switzerland were DES.[30]

Restenosis (growth of vascular smooth muscle tissue) is a common adverse event of concern to PCI.[39] The strut thickness of the stent is key in reducing restenosis.[44] DESs also chemically prevent restenosis, whereas the other two technologies offer drug-free treatment.[37-39] DESs are coated with medications that inhibit cell proliferation and activate signal transduction pathways.[38,39,43] The challenge of restenosis (and accompanying chronic inflammation) are decreased in DEBs compared to DESs, as no stent polymer or stent scaffolding are implanted into an arterial wall.[41,42] After the delivery of the pharmaceutical and plaque compression by the balloon, the artery can retake its original shape with minimal disturbance and diminish the possibility of abnormal arterial flow.[42]

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).[45,46] The procedure generally involves the heart being accessed through the use of full sternotomy (dividing or 'cracking' the sternum).[47] Various techniques can be used to conduct a CABG procedure. These techniques include the use of a cardiopulmonary bypass machine or performing a minimally invasive surgery.[47,48]

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).[14,45,46,49] Grafts from saphenous vein are often used because the conduits can easily be harvested from the patient's legs. The superiority of either graft will not be addressed in the HTA as it is beyond the scope of the research questions (***Section 2***).

Use of a cardiopulmonary bypass machine

CABG may be performed with or without the use of a cardiopulmonary bypass machine (i.e. 'on-pump' vs 'off-pump').[47,50] The machine provides the option of a bloodless surgical field as it can artificially circulate oxygenated blood throughout the patient's body after the heart has been stopped (i.e. cardioplegic arrest).[47,50] A patient's heart is not stopped during an off-pump CABG procedure.[47,51] Instead, other stabilisation techniques are used and the necessary coronary anastomoses are performed on the patient's beating heart.[47,50,51] Typically, a CABG procedure is performed on-pump unless it is deemed unsafe due to the individual clinical presentation (e.g. calcification of the aorta, which prevents aortic clamping).[47,52,53] This is because cardiopulmonary bypass has been previously associated with an increased risk of post-surgical morbidity in patients with comorbidities (e.g. diabetes mellitus (type 1 and 2), chronic kidney disease, COPD, obesity).[47,54] This was supported by clinical experts, as they stated that off-pump procedures are generally only performed on high-risk patients when it is too dangerous to place them on cardiovascular bypass.

Minimally invasive direct coronary artery bypass grafting

Minimally invasive CABG procedures (referred to as a minimally invasive direct coronary artery bypass grafting [MIDCAB]) are infrequently performed and are generally reserved for a subpopulation of CCS patients.[48,54,55] Unlike a standard CABG, the procedure avoids a full sternotomy and the use of the cardiovascular bypass machine.[54,55] The procedure is used to treat CCS patients that have complex lesions and/or stenosis (both single vessel and multivessel) in the left anterior descending artery (LAD), because treatment with PCI or standard CABG is deemed too risky.[55] Given that a MIDCAB procedure is usually performed on a high-risk patient, a cardiopulmonary bypass machine is not used.[48,54,55] During the procedure, the LAD is accessed through 5–6 cm incision made in the fourth or fifth left intercostal space.[54] The graft for the procedure is harvested from the left IMA at the level of the first rib.[54] Then the anastomosis of the conduit grafted from the IMA to a stabilised LAD is performed on a beating heart.[54,55]

4.2 Non-invasive treatment

4.2.1 Optimal medical therapy

OMT (also known as pharmacological management) is a systemic and conservative form of treatment for CCS.[1] The pharmaceuticals are used alongside invasive coronary surgery to treat CCS patients. Nonetheless, OMT can also be used as a standalone treatment.[1,23] It is recommended that patients are monitored for 2–4 weeks after the commencement of OMT to review their response to the therapy.[1] There is no universally accepted treatment regimen of OMT for CCS patients, because the prescribed medical therapy is patient-specific and based on intolerances, contraindications, and comorbidities.[1,23,56] The 2019 ESC guidelines determine how OMT is prescribed to CCS patients in Switzerland. Therefore, OMT detailed in these guidelines is described below and will be used as the standard definition of OMT described in the PICO criteria (***Section 5***).[1]

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

The drug classes, individual drugs, and drug applications recommended by the ESC to treat CCS patients are detailed below:[1]

- **Antiplatelet therapy:** prevents blood clot formation by stopping platelets from sticking together.
    - **Oral P2Y12 inhibitors:** prasugrel and ticagrelor act as antiplatelet therapy for patients who have experienced acute coronary events.
    - **Vitamin K antagonist (VKA):** inhibits vitamin K production in the liver, which decreases the availability of vitamin K to aid in coagulation.[57,58] Common VKAs used in Switzerland include phenprocoumon and acenocoumarol. Warfarin is not available in Switzerland.[59]
- **Anti-ischaemic/anti-anginal therapy:** relieves angina and ischaemic symptoms.
    - **Beta-blockers**: for angina relief and reducing morbidity and mortality from CCS. Beta-blockers are indicated in patients with left ventricular dysfunction, heart failure, or previous ST-elevation MI. Bisoprolol or metoprolol are preferred for the treatment of CCS patients.[2]
    - **Calcium channel blockers (CCB)**: antianginal therapy for the relief of ischaemia or angina and to control heart rate. Amlodipine is the most common CCB used in Switzerland to treat CCS. On occasion verapamil and diltiazem are also used in Switzerland.[1,2,60]
        - **Non-dihydropyridine (DHP)-CCB:** reduce heart rate due to the drug being more myocardially-selective. Popular non-DHP- CCBs include verapamil and diltiazem.[61,62]
        - **Dihydropyridine (DHP)-CCB:** May be effective for the treatment of angina where symptoms are not resolved with beta-blockers or CCB. DHP-CCB reduces heart rate

being vascular selective. Therefore, it is a first-line therapy in patients presenting with low resting heart rate. Examples of DHP-CCB drugs include nifedipine and amlodipine.[2]

- **Nitrates**: Short acting nitrates (e.g. sublingual and spray nitro-glycerine) are available for the immediate relief of angina symptoms. Long-acting nitrates (e.g. nitro-glycerine, isosorbide) are prescribed as a second-line treatment when DHP-CCB do not provide symptom relief, are not well tolerated by patients, and/or are concraincidated.[1] Other nitrates used to treat CCS include ranolazine, nicorandil and ivabradine.

- **Renin angiotensin system blockers:** relax veins and arteries, which in turn lowers a patient's blood pressure and makes it easier for their heart to pump blood.
  - **Angiotensin-converting enzyme (ACE) inhibitors**: enzyme inhibitors used to relax veins in high-risk patients; primarily prescribed to individuals with concurrent hypertension, LVEF ≤ 40%, diabetes mellitus (type 1 and 2), or chronic kidney disease.
  - **Angiotensin receptor blockers (ARBs):** For patients with an intolerance to ACE inhibitors, ARBs may be an appropriate substitute. The combination of ARBs and ACE inhibitors may lead to an increase of renal adverse events in hypertension patients, so is not recommended.
- **Lipid-lowering therapy:** reduce cholesterol.
  - **Statins:** blocks the enzyme that the liver uses to produce cholesterol. Common statins include, atorvastatin, rosuvastatin, simvastatin, pravastatin, fluvastatin, pitavastatin, and pravastatin.[2] The goal stipulated by the ESC guidelines is to reduce LDL-C by 50% from baseline. In patients who have experienced a second event within two years, a lower target may be set.[1]
  - **Ezetimibe:** reduces the amount of cholesterol absorbed through a patient's diet. [63] The 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:** PCSK9-inhibitors (i.e. evolocumab, alirocumab) are lipid-lowering drugs that can reduce LDL-C by binding to LDL receptors and causing the lysosomal degradation.[64] These drugs are generally prescribed to patients who do not meet LDL-C targets using statin 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 dual antiplatelet therapy and are likely to require less antianginal medication. Conversely, patients treated with OMT alone may require more antianginal therapy and fewer antiplatelet drugs.

A small study in a Swiss CCS population (2008) found almost all patients with CCS were prescribed antiplatelet therapy (98.6%).[65] Statins (84%), beta-blockers (75%), calcium antagonists (34%), and nitrates (51%) were also commonly administered.[65]

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 also a vital part of CCS treatment.[1,23] However, regardless of the importance of lifestyle modifications to a CCS patient's overall treatment regimen, they will not be considered in the HTA as it is beyond the scope of the research questions (***Section 2***).

5 Population, intervention, comparator and outcomes

Table 1 PICO criteria

Population	Adults diagnosed with symptomatic CCS [a] *Exclusion criteria: ACS-naïve patients with no symptoms of CCS, ACS patients, or patients that experienced MI or unstable angina in the past 12 months*
Intervention	Invasive procedure(s) plus OMT: 1) CABG + OMT 2) PCI + OMT, including: a. Angioplasty with 3rd generation drug-eluting stent (DES)+ OMT b. Drug-eluting balloon (DEB) angioplasty + OMT *Exclusion criteria: CABG with concurrent PCI*
Comparator	Any OMT administered to reduce the risk of cardiac events and relieve symptoms (angina and ischaemia) [b]
Outcomes	**Clinical outcomes** • MACE – composite of: all-cause mortality, MI, revascularisation, hospitalisation or stroke • All-cause mortality • Health-related quality of Life (HRQoL) o General HRQoL measures (e.g. SF-36) o Cardiac-specific HRQoL (e.g. SAQ-7) • Hospitalisation (i.e. acute myocardial infarction [MI], stroke [incl. ischaemic, haemorrhagic], heart failure) [c] • Revascularisation • Total adverse events • Serious adverse events (including stroke) **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; **CTO**: chronic total occlusion; **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.

Notes:

[a] Signs and symptoms include: ischemia; 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 three months (chronic total occlusion [CTO]).[1,15,16]

[b] 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).

[c] Eligible new hospital admission for patients with coronary heart disease will be limited to the International Consortium for Health Outcomes Measurement (ICHOM) definition.[66]

5.1 Population

The population of interest includes 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.[1,67] CCS patients that are considered at a high risk of having an acute event (e.g. those with comorbidities, multivessel disease or left main coronary artery disease) will be included. Similarly, patients that had previously undergone revascularisation procedures will be included. In addition, ACS-naïve patients (i.e. reduced oxygen supply to the heart) with no symptoms of CCS will be excluded, because they are generally not eligible for PCI or CABG in clinical practice. The reason for this ineligibility is that the patients tend to have poor outcomes after undergoing PCI or CABG.[20,32] No limitations will be 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 will be limited to include angioplasty (including DEB only) with or without stenting (only third generation DES). Similarly, CABG will include 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 will be placed on composition of the CABG graft (i.e. complete [arterial] graft or partial [arterial/vein] graft) or where the CABG graft was harvested from (e.g. mammary, saphenous, etc.). Studies that include CABG with concurrent PCI will be excluded.

5.3 Comparator

The relevant comparator is OMT; because OMT regimens are idiosyncratic, it is not possible to predetermine a clear definition.[1,56] Given that OMT will be administered in both study arms – intervention and comparator – it is not essential that OMT is clearly defined in the included studies. However, a limitation will be placed on OMT to ensure that the treatment in the included studies is in line 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 relive angina symptoms, improve quality of life, and reduce mortality and cardiac morbidity (i.e. MI and low LVEF).[1,20,68] Therefore, only clinically important effectiveness outcomes will be 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):[66]

MACE is a composite endpoint that is routinely used to evaluate clinical outcomes of cardiovascular interventions.[69-71] However, there is no clear definition of MACE, because the composition and relatedness of the included outcomes differ between settings and study designs.[71] These varying compositions often makes it difficult to compare MACE between studies.[71] For the purposes of the HTA, MACE will only include all-cause mortality, MI, revascularisation, hospitalisation and stroke. Clinical experts have suggested these components are commonly used to defined MACE within the Swiss healthcare context.

All-cause mortality will reflect 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 can provide patient-centred information on physical, social, emotional and mental health, to guide clinical practice.[66,72] The tools used to quantify and gather patient-centred information can be disease-specific or generic.[66,72] Examples of disease-specific HRQoL 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) and the Quality of Life after Myocardial Infarction (MacNew) questionnaire.[66] Similarly, examples of tools that measure general HRQoL include the European quality of life five dimension (EQ-5D) and short form-36 (SF-36).[73] No limitations will be placed on the type of HRQoL tools included.

Hospitalisation is a common indicator of disease progression.[66] Hospitalisation can provide an objective measure of the severity of the disease impact on patients. Hospitalisation will be limited to MI, stroke (including haemorrhagic and ischaemic), and heart failure.[66]

Subsequent coronary artery revascularisation can occur in CCS patients that have previously undergone invasive coronary artery surgery (CABG or PCI).[66]

Adverse events are defined as temporary, non-life-threatening, unintended responses associated with a medical intervention (e.g. a surgical procedure or pharmaceutical).[74] An adverse event does not necessarily need to have a clear causal relationship with the medical intervention. Adverse events

generally include an increase in disease severity, and/or the development of new symptoms or signs (including new disease).[74]

Serious adverse events are unfavourable experiences associated with a medical intervention may be life-threating at the time of occurrence.[74] The incidents do not need to have a causal relationship with the medical intervention to be considered a serious adverse event.[74] For this HTA, serious adverse events may need to be subdivided into four categories: events caused by pharmaceuticals; acute surgical complications; major surgical complications (CABG only); and interventional cardiology complications (PCI only).[66,74] The surgical complications will be defined and delineated according to the standardised outcome measurements for CCS detailed by ICHOM.[66] The International Council for Harmonisation definitions for serious adverse events will be used to define serious adverse events caused by pharmaceuticals.[74]

6 HTA key questions

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

6.1 Additional questions

1. Is the safety and effectiveness of PCI plus OMT and CABG plus OMT versus OMT alone in CCS affected by characteristics impacting patient risk? These populations include:
    a) Comorbidities that classify CCS patients as high risk (i.e. cardiovascular comorbidities [incl. hypertension, valvular heart disease, heart transplantation], non-cardiovascular comorbidities [incl. cancer, diabetes mellitus (type 1 and 2), obesity, chronic kidney disease, elderly])
    b) Sex/ gender
    c) Refractory angina
    d) Left main coronary artery (LMCA) stenosis > 50%
    e) Left ventricular ejection fracture (LVEF ≤ 40%)
2. Is the safety and effectiveness of PCI plus OMT and CABG plus OMT versus OMT alone in CCS affected by prior revascularisation (with either PCI or CABG)?

7 Methodology

7.1 Clinical evaluation

The proposed methods have been developed with reference to the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)*,[75] and presented in accordance with the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[76]

7.1.1 Databases and search strategy

Systematic literature searches will be conducted in five biomedical databases – PubMed (MEDLINE), Embase (Ovid), the Cochrane Library, the INAHTA database and EconLit. Preliminary search strings are presented in ***Appendix A***. During the HTA phase of this project, the PubMed (MEDLINE) search strategy detailed in ***Table 4*** will be adapted to Embase (Ovid) and the Cochrane Library. Search filters to exclude non-human studies, and specific publication types (i.e. editorials, letters to the editor, news articles, and conference abstracts) will be utilised in all searches. The searches will be designed to capture English, French, German, and Italian publications. Grey literature searches will be limited to searching HTA and specialist cardiology websites (***Table 8*** in ***Appendix A***). The International Clinical Trials Registry Platform (ICTRP) will be searched to identify relevant unpublished and/or ongoing clinical trials. Preliminary search strategies for clinical trial registers are listed in

Table 6 in ***Appendix A***.

Given the constant development in PCI, CABG and OMT, the searches will be limited to include studies published after 1 January 2010. This date was selected because this is around the time that the current era of PCI, CABG, and OMT started.[38,39,45,48,53,77,78] This date range was endorsed by a Swiss clinical expert. Trials published before this date will include PCI, CABG, and OMT that are not representative of technology, techniques, and population that are currently used in contemporary clinical practice in Switzerland.

7.1.2 Study selection

All results from systematic literature searches will be imported into Rayyan (Rayyan Systems Inc, United States) for study selection.[79] Rayyan allows for blinded title and abstract screening of citations between independent reviewers, and resolution of study inclusion conflicts.[79] Screening will be performed to include studies that meet the pre-defined study selection criteria (***Table 2***). Only studies published in World Health Organization (WHO) Mortality Stratum A will be included.[80] This limitation will ensure that all included studies have a comparable disease burden and cause of death to Switzerland.[80] Exclusion criteria will be 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, or 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
	• PCT + OMT, including:
	  ○ 3rd generation DES + OMT
	  ○ DEB angioplasty + OMT
		Balloon angioplasty
		BMS
		1st and 2nd generation DES
		CABG with concurrent PCI

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

Outcomes	**Clinical outcomes**
	• MACE – composite of: all-cause mortality, MI, revascularisation, hospitalisation or stroke
	• All-cause mortality
	• Health-related quality of Life (HRQoL)
	  ○ General HRQoL measures (e.g. SF-36)
	  ○ Cardiac-specific HRQoL (e.g. SAQ-7)
	• Hospitalisation (i.e. acute myocardial infarction [MI], stroke [incl. ischaemic, haemorrhagic], heart failure) [c]
	• Revascularisation
	• Total adverse events
	• Serious adverse events (including stroke)
	Health economic outcomes
	• Budget impact
	• Cost-effectiveness/cost-utility
		Inadequate data (e.g. no measures of variance, incongruous data reported between figures and text, etc), incomplete reporting, unclear follow-up duration, any other outcomes

	Inclusion criteria	Exclusion criteria
	• Direct medical costs of the technology and associated services	
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 analysis • Cost analysis	• Single arm studies • Case reports • Conference abstracts • Letter to the editor • Expert opinion • Editorial • Narrative review articles
Language	English, German, Italian, French	All other languages
Country	WHO Mortality Stratum A countries: 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	Non-Stratum A countries
Date	Studies published on or after 1st of January 2010	Studies published on or before 31st December 2009

Abbreviations:

ACS: acute coronary syndrome/symptoms; **CABG**: Coronary artery bypass graft; **CCS**: chronic coronary syndrome; **CTO**: chronic total occlusion; **DEB**: drug eluting balloon; **DES**: drug eluting stent; **MACE**: major adverse cardiac events; **MI**: myocardial infarction; **OMT**: optimal medical therapy; **PCI**: percutaneous coronary intervention; **SAQ-7**: **SF-36**: Short-Form 36; **WHO**: World Health Organization.

Notes:

[a] Signs and symptoms include: ischemia; 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 three months (chronic total occlusion [CTO]).[1,15,16]

[b] OMT regimens are patient-specific, and account for drug intolerances, comorbidities, and non-adherence issues. As OMT is administered in both study 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] The aim is to avoid including studies that are not applicable to the Swiss healthcare system (e.g. use of novel drugs or inappropriate drug combinations).

[c] Eligible new hospital admission for patients with coronary heart disease will be limited to the ICHOM definition.[66]

The search results will be screened by title and abstract by two reviewers blindly. To ensure the selection criteria are interpreted consistently between reviewers, two individual screening samples (k = 250 and k = 250 citations) will be screened by both reviewers in duplicate to calculate inter-rater reliability. The first sample of citations (k = 250) will be a training sample only, while the second sample will be used to calculate inter-reliability (Fleiss Kappa).[81] An inter-reliability score of 0.7 or higher (Kappa ≥ 0.7) indicates substantial agreement between the reviewers.[82,83] Where the inclusion of a study is unclear, the full text will be reviewed. From the completion of title and abstract screening, the full-text publications will be reviewed by each reviewer independently. Conflicts regarding final study inclusion will be settled by a third reviewer. The inclusion and exclusion decisions will be detailed in a PRISMA flow chart.[76]

Study design

Different types of study designs will be considered for inclusion. Contemporary systematic reviews and meta-analyses that meet the PICO criteria (***Table 1***) will be included to assess the clinical outcomes associated with PCI (with OMT) and CABG (with OMT) compared to OMT alone. RCT evidence will be

included in the absence of, or to update, existing systematic reviews and meta-analyses. If there is limited evidence for adverse events associated with invasive coronary artery surgery (CABG or PCI) with concurrent OMT, non-randomised studies of interventions (NRSI) that meet the PICO criteria (***Table 1***) will also be included.

7.1.3 Data extraction

Data will be extracted (on study-arm-level) from included publications by a single reviewer using a standardised template, which will be adapted according to the design of the included studies. Data checking will be performed against the original publication by a second reviewer. Conflicts between will be resolved by consensus. If consensus cannot be reached, a third independent reviewer will be consulted. Data to be extracted include:

- **study information:** author, country, publication date, randomisation technique (RCT 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.
- **additional noteworthy factors:** possible effect modifiers (e.g. type of PCI), limitations or key differences of the study.

Where data is presented in a graphical format instead of numerically, the data will be estimated using WebPlotDigitizer.[84]

7.1.4 Analysis of study quality

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

The quality and risk of bias tools used to appraise the included studies was dependent on the study design. Systematic reviews will be evaluated against the AMSTAR-II appraisal criteria.[85] RCTs will be

evaluated with the Cochrane Risk of Bias 2.0 (RoB 2.0) tool.[86] The Cochrane Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool will be applied to NRSI.[87]

The Grading of Recommendation, Assessment, Development and Evaluations (GRADE) approach will be used to evaluate the quality of the evidence used to calculate the overall effect size for each of the seven prioritised outcomes.[88,89] The five domains (imprecision, inconsistency, indirectness, risk of bias, and publication bias) of the GRADE framework will be scored ('high', 'moderate', 'low' and 'very low') according to an decision algorithm developed by Pollock et al.[88,90].[88,90] The overall strength of the evidence (overall GRADE score) associated with the effect sizes for each outcome will be presented in summary of findings (SoF) tables generated in GRADEpro.[89,91]

7.1.5 Data analysis of efficacy, effectiveness, and safety outcomes

Data synthesis

The method of data synthesis will depend on whether relevant systematic reviews and meta-analyses are available. *De novo* analysis will not be performed if existing systematic or meta-analyses meet the inclusion criteria. In such cases, the results from the existing studies will be reported for the relevant outcomes outlined in ***Table 1***, and synthesised into a GRADE SoF table.

In the absence of existing systematic reviews and meta-analyses, a *de novo* analysis of primary studies will be conducted. The statistical method used to synthesise primary studies will depend on the amount of data available; where there are at least 10 studies reporting an outcome, mixed-effect pairwise meta-regression models that incorporate follow-up duration as a covariate will be used to analyse the data.[92-94] This model type enables clinical outcomes to be reviewed over the complete follow-up period and not just at specific timepoints.[92,93,95] This will enable the meta-analysis to compare the short-term benefits of a PCI and OMT or CABG and OMT against the long-term benefits of OMT. This type of model is also referred to as a 'longitudinal meta-analysis'.[92,95]

If there are insufficient data points to perform mixed-effect meta-regression models, pairwise meta-analyses that use random-effects models will be used to compare PCI and OMT or CABG and OMT against OMT for both continuous and dichotomous outcomes reported by at least 2 studies. For the short-term benefits of PCI (and OMT) and CABG (and OMT) to be compared against the long-term benefits of OMT, five time points – of 30 days, 1 year, 5 years, 10 years and more than 10 years – will be used. The 30 days timepoint will be limited to reporting the point estimates for HRQoL, adverse events, and serious adverse events. These predetermined timepoints have been selected following input from clinical experts and ICHOM guidance.[66]

Given that it is not possible to include the personalised nature of OMT into the planned meta-analyses techniques, it will be assumed that all OMT is equivalent between treatment groups, and across trials. For the purpose of the clinical evaluation, the equivalency will be extended to two scenarios. The first

scenario includes OMT prescribed per before and after revascularisation; the second scenario includes, OMT prescribed alone, compared to OMT prescribed alongside concurrent revascularisation.

Random-effects models will be used to account for variation between the various combinations of surgical procedures (CABG, PCI [BMS, DES]) and medications (e.g. antiplatelet therapy and anti-anginals) in OMT.[75,95] A random-effects model will be used to account for variations in the populations and interventions used across the included studies.[75,95]

Only one continuous outcome is included in the PICO (HRQoL), which will be analysed as either a mean difference or standardised mean difference (SMD) with 95% confidence intervals (CI). SMDs will be used if there are differences in the measurement scales used to report HRQoL across individual studies. The SMDs will be interpreted following the recommendations detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (*version 6.2*), whereby SMD of 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.[75] In addition, SMDs will be re-expressed as the most reported scale of HRQoL included in the analysis.[75]

Dichotomous outcomes will be evaluated as risk ratios with 95% CIs. In a situation where NRSIs are included, adverse event data will be meta-analysed (if possible) and reported as risk ratios with 95% CIs, noting that the risk of confounding in these study designs is high. If it is not possible to meta-analyse these study types, the results will be described narratively.

Assessment of heterogeneity

Heterogeneity and inconsistency (pairwise or mixed-effect meta-regression) will be assessed statistically. The statistical methods that will be used to measure heterogeneity in both continuous outcomes and dichotomous outcomes are the Tau^2 and I^2 statistics. The I^2 statistic will be interpreted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (0–40% is possibly not important; 30–60% is moderate; 50–90% is substantial; and 75–100% is considerable heterogeneity).[75] The significance of I^2 will depend on the strength of the evidence for heterogeneity (i.e. Tau^2 and Chi^2) as well as direction and size of the measured effect.[75] In situations where considerable heterogeneity is evident, it will be explored with either a meta-regression or subgroup analysis.

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

If there are too few data points to perform a mixed-effect meta-regression model, a pairwise meta-analyses will be conducted, and the outcomes will be presented in a forest plot that visualises the effect size and variance at the predetermined timepoints.

Subgroup and sensitivity analysis

A variety of techniques (i.e. subgrouping, meta-regression, sensitivity analyses) will be used to investigate possible effect modifiers (e.g. high-risk patients, risk of bias, etc.).

Subgrouping will be used to explore a subset of participants (e.g. high-risk patients) or study characteristics.[75] The subgroup analyses will use random effects models with an assumption of a normal distribution. A two-tailed Z-test will be used to determine if the difference between the two groups is statistically significant. The difference between subgroups will be considered statistically significant if there is less than 5% of difference occurring by chance alone (i.e. $p < 0.05$). Given that none of the subgroup analyses include two or more groups, a Q-test will not be performed. If there are only 10 trials in the subgroup analyses Tau^2 will be calculated using trials in both subgroups. However, if the subgroup analyses included more than 10 trials, a separate Tau^2 will be calculated for each individual subgroup.

Meta-regressions will be performed to review the impact of effect modifiers on the outcomes detailed in the PICO criteria (***Table 1***). Meta-regression will only be performed for outcomes with a minimum of 10 studies.[75] The meta-regressions will use random effects models with an assumption of a normal distribution. If the covariate in question is categorical (e.g. type of PCI), dummy values will be used to ensure a meta-regression can be performed. The impact of the covariate (i.e. effect modifiers) on the effect size for each outcome will be reported as the slope of the meta-regression. For continuous outcomes the regression slope will be expressed as the unit of analysis (e.g. SMD). However, for dichotomous outcomes, the regression slope will be expressed as a log of RR (ln[RR]). The impact of the covariate (i.e. effect modifiers) on the effect size will be tested for statistical significance using a two tailed Z-test. If there is less than 5% chance of the slope occurring randomly (i.e. $p < 0.05$), it will be considered statistically significant. Given that none of the meta-regression include two or more covariates, a Q-test will not be performed. The proportion of variance (between study heterogeneity) explained by the relationship between a covariate and its point estimate, will be determined using R^2. Individual bubble-plots with a fitted meta-regression line will be used to illustrate the relationship between a covariate and its effect size, for each outcome.

Finally, sensitivity analyses will be 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. The sensitivity analyses will follow parameters listed above. Possible sources of uncertainty include risk of bias and imputed SD.[75]

The effect modifiers that will be explored a priori are listed below:[1]

Subgroup

- Comorbidities that classify CCS patients as high risk (i.e. cardiovascular comorbidities [incl. hypertension, valvular heart disease, heart transplantation], non-cardiovascular comorbidities

[incl. cancer, diabetes mellitus (type 1 and 2), obesity, chronic kidney disease, elderly – over 75])

- 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 (e.g. SD)
- Risk of bias due to missing outcomes
- Risk of bias due to publications bias
- Risk of bias due to selection bias

It is important to note that the effect modifiers investigated may change during the analysis phase of the full HTA.

Assessment of publication bias

The risk of publication bias will be assessed by using tests for funnel plot asymmetry.[96] The funnel plot tests will only be performed for outcomes with a minimum of 10 studies.[75] In addition, publication bias will be assessed through searching clinical trial registries to identify unpublished trials. The findings will be described narratively.

Imputation methods for dealing with missing values

Missing standard deviations (SDs) will be imputed from available means, sample sizes, standard errors and 95% confidence intervals (95% CIs) using formulas detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (*version 6.2*).[75]

If continuous values need to be combined, formulas detailed in the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)* will be used.[75]

If the required data are not available to calculate SDs, they will be imputed using the 'impute_SD' function in *R Studio* (*R* version 3.0.1) package 'metagear', following the imputation methods described by Braken et al. (1992).[97-100]

For studies that report outcomes graphically, WebPlotDigitizer will be used to convert graph points into numerical values.[84]

7.2 Economic evaluation

To inform the methodology of the economic evaluation, the economic literature will be systematically reviewed: (1) to identify any existing Swiss economic evaluations addressing the research question, and (2) in the absence of such studies, to identify relevant literature to guide an independent economic evaluation.

7.2.1 Review of the economic literature

The systematic literature searches described in ***Section 7.1.1*** will be used to identify relevant cost, cost-effectiveness, and budget impact studies. Screening will be performed as outlined in ***Section 7.1.2*** to identify studies aligned with the PICO criteria (***Table 1***). Only studies performed in WHO Mortality Stratum A will be included,[80] in order to capture populations representative of Switzerland. During initial screening, cost analyses, economic evaluations and budget impact analyses will all be included to identify studies relevant to research questions 2, 3, and 4 (***Section 6***).

To inform the methodology used to address research question 3 (***Section 6***), full economic evaluations (studies that value both costs and benefits of different treatments) will be grouped and prioritised for data extraction. Data pertaining to the following domains will be extracted: evaluation type, model used (if relevant), population considered, intervention and comparator, country, perspective, time horizon, effectiveness measure, key assumptions, and study findings. Included studies will also be assessed for applicability to the Swiss context and review question.

In the case Swiss-specific evidence is retrieved, critical appraisal using an appropriate checklist (e.g. the Drummond checklist; the Consolidated Health Economic Evaluation Reporting Standards [CHEERS] checklist; the Philips checklist for decision-analytic models)[101-103] will be undertaken to determine its usefulness for decision making. If available evidence is sufficient for decision makers, study results would be reported narratively.

In the absence of current economic studies that address the research question within the Swiss context, an independent economic evaluation is the preferred approach due to limitations of applying evaluation results from other healthcare settings. This evaluation would be guided by existing peer-reviewed literature in the field. Data extracted from the included studies would inform the evaluation methodology; however, critical appraisal of the included studies would not be undertaken because no conclusions would be drawn from the extracted data. Any assumptions borrowed from the existing literature would be critically assessed. Initial scoping suggests an independent evaluation will likely be required, although this will be confirmed following the systematic literature searches. Below, we outline key methodological considerations for an independent evaluation, should this be required.

7.2.2 Methodological considerations for an independent economic evaluation

The two interventions − PCI with OMT and CABG with OMT − will be individually assessed against OMT alone. Analyses of CABG with concurrent PCI stenting and CABG versus PCI stenting are out of scope for this HTA.

The analysis will most likely use a state transition model to demonstrate the transition of patients through the various health states associated with CCS; however, this will be confirmed during the HTA. The health states of interest include CCS, individual MACE outcomes, and death.

Results of the clinical evaluation will inform the clinical input parameters of the economic model. Where data are unavailable, these figures will be supplemented by data from peer-reviewed literature and databases.

Perspective

The analysis will be conducted from a Swiss healthcare payer perspective as this is the relevant perspective for the decision maker. Direct medical costs for services covered by Swiss mandatory health insurance will be included, irrespective of the actual payer (which may include health insurers, other social insurance, the government, or patients). Non-medical and indirect costs will not be included (e.g. travel costs, informal care or productivity losses).

Population

The economic model will reflect Swiss patients with symptomatic CCS. The population will include both intervention-naïve CCS patients (no prior interventions) and CCS patients with a history of PCI or CABG revascularisation. During the HTA, it will be assessed whether healthcare costs and/or clinical outcomes differ between patients with and without a prior intervention. If significant differences are identified, subgroup analysis would be considered.

Two separate patient cohorts will be defined for the two individual assessments of cost-effectiveness (PCI with OMT versus OMT alone; CABG with OMT versus OMT alone). Patient characteristics in the identified clinical studies will be compared to the Swiss context during the HTA.

As an example, the SWISS-II study is one source that may provide information on the demographics (age, sex, risk factors/comorbidities, and prior PCI) of patients with CCS in Swiss practice.[104,105] In the case where Swiss specific data is unavailable, data from neighbouring countries (France, Germany, Austria, Italy) in peer-reviewed literature may also be considered.

Intervention and comparator

The interventions to be included are PCI with OMT and CABG with OMT. These interventions will be compared with OMT alone.

OMT is administered in both the intervention and comparator groups; however, OMT regimens differ slightly between patients on OMT alone and patients after revascularisation.[1] Patients on OMT alone have single antiplatelet therapy with higher antianginal medication load. Patients after revascularisation require less antianginal medication but will be prescribed dual antiplatelet therapy. Besides 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. The complete cessation of antianginal therapy is rare, apart from a period immediately after CABG. In this population, there may be reuptake in symptomatic patients. It is important that the economic analysis can capture differences in OMT use between intervention and comparator groups for costing purposes.

Other specifics of OMT (e.g. drug intolerances; non-adherence issues) will likely be considered negligible (per the PICO criteria, ***Table 1***). Nonetheless, the impact of such issues on the clinical

outcomes (e.g. revascularisation; adverse events) would be accounted for within the clinical input parameters.

The use of OMT in patients undergoing PCI, CABG, or OMT alone will be sourced from the included RCT evidence. The medication classes to be considered include aspirin, beta-blockers, ACE inhibitors, statins, CCBs, $P2Y_{12}$ inhibitors and nitrates. While every attempt to present a comprehensive view of OMT will be made, the estimation of the use of some medications may be limited by inconsistent reporting.[106] These medications may be excluded from the analysis entirely (i.e. across both intervention and comparator arms) if meaningful cost values cannot be estimated. OMT will be recognised at the drug class level; therefore, we will estimate a unit cost for each drug class. The applicability of OMT resource use within the included RCTs to Swiss practice will be explored during the HTA.

Outcome of the analysis

The proposed approach will most likely be a cost-utility analysis (CUA). Effectiveness will be expressed using the quality-adjusted life year (QALY). Health state utilities may be informed by the quality-of-life data captured in the clinical review or sourced from other peer-reviewed literature. If HRQoL outcome data were available from the clinical evaluation, this would be assessed for relevance to the economic evaluation. Where HRQoL was expressed using a non-preference-based instrument, the availability of a mapping algorithm to transform the data into utilities would be considered. We would also consider the time horizon over which HRQoL data is available, and whether the data would provide overall estimates of QALYs gained or inform utility values applied to health states of a model. Alternatively (or supplementarily), externally sourced utility weights may be required—these would be applied to time spent in different health states to estimate QALYs gained. Mortality outcomes may be derived from the clinical section of the report and general population data (i.e. Swiss life tables).

Costs (resource use and unit costs) will be estimated using a combination of sources, including peer-reviewed literature, clinical care guidelines, Swiss diagnosis-related group (DRG) costs, TARMED positions, and the Spezialitätenliste. Costs will be estimated for the following items: PCI and CABG procedures, the associated hospital stay, OMT, follow-up, and the management of any adverse events or clinical events included in the model (yet to be finalised), such as revascularisation, MI and stroke.

Incremental cost-effectiveness ratios will be expressed as the cost per QALY gained. One-way deterministic sensitivity analysis and probabilistic sensitivity analysis will be undertaken to explore the impact of uncertainty in input parameters on the economic results. The probability of cost-effectiveness will be expressed as a function of willingness to pay (WTP).

Summary

In the absence of existing contemporary economic modelling relevant to the research question from the perspective of the Swiss healthcare payer, an independent economic evaluation will be performed.

Existing published models reflecting a similar patient population would act as a foundation for the independent economic evaluation. Details contributing to the structure of the proposed evaluation are outlined in ***Table 3***.

Table 3 Summary of the proposed economic evaluation methodology

Perspective	Swiss healthcare payer
Patient population	Adults diagnosed with symptomatic CCS
Intervention	CABG + OMT or PCI + OMT
Comparator	Any OMT administered with the objective to reduce risk of cardiac events and relieve symptoms (angina and ischaemia)
Type of economic evaluation	CUA
Time horizon	Lifetime
Sources of inputs	Published meta-analyses, RCTs, observational studies, Spezialitätenliste, Analyseliste, TARMED, Swiss DRGs, expert opinion
Costs	Direct medical costs of revascularisation and OMT (CHF) Direct medical costs of patient follow-up and their clinical outcomes (revascularisation, coronary angiography, non-invasive diagnostic testing, outpatient visits, hospitalisations, adverse events)
Effect measure	QALYs
Discount	3% p.a. for both costs and QALYs

Abbreviations:
CABG: coronary artery bypass graft; **CCS:** chronic coronary syndrome; **CHF:** Swiss francs, **CUA:** cost-utility analysis, **DRG:** diagnosis-related group; **OMT:** optimal medical therapy, **PCI:** percutaneous coronary intervention; **QALY:** Quality-adjusted life year; **RCT:** randomised controlled trial
Notes:
OMT is patient-specific and will be assessed at the drug class level in the economic evaluation.

7.2.3 Budgetary impact analysis

The budget impact analysis (BIA) will be performed from the perspective of the Swiss healthcare payer. The size of the target population – symptomatic Swiss patients with CCS utilising the intervention (revascularisation procedures) – will be estimated using the TARMED or the Swiss DRG databases, supplemented with additional sources. Revascularisation procedures may be billed using either TARMED tariffs (PCI: 17.1110 to 17.1190) or Swiss DRGs (CABG: F06A, F06B, F06C, F06D; PCI: F24A, F24B, F24C, F24D, F24E, F24F). These codes are applicable for indications other than CCS; therefore, further information will be needed to estimate the size of the target population. For example, data from all 36 Swiss interventional cardiology centres (2018) provides information on the uptake of percutaneous cardiac procedures (including PCI) in Switzerland and may be used to inform current usage of PCI in CCS.[30]

The projected costs (CHF) to the Swiss healthcare payer for revascularisation procedures in patients with CCS over a 5-year period under current policy and practice conditions will be evaluated.

A BIA may be undertaken to examine the financial implications of policy change (e.g. limiting the indication for reimbursement). The decision whether to perform such an analysis will be made in conjunction with the clinical and economic findings. As OMT regimens are different for patients who do

or do not have revascularisation (see ***Section 7.2.2***), a substitution of revascularisation procedures with OMT alone could impact the cost of OMT for patients making the switch. OMT costs for patients after revascularisation and on OMT alone would be included in the BIA, and would be informed by results of the economic evaluation. Analysis into the safety and effectiveness of the intervention for high-risk subgroups may guide decisions around providing limitations of the services.

7.3 Legal, social, ethical, and organisational issues

The systematic literature searches detailed in ***Section 7.1.1*** will be used to identify literature relevant to the legal, social, ethical, and organisational issues related to PCI, CABG and OMT in symptomatic patients with CCS. Additional, targeted, non-systematic keyword searches for literature that addresses these domains will be conducted (***Table 8*** in ***Appendix A***). Systematic reviews, literature reviews, RCTs, non-randomised studies, single-arm studies, ethnographic studies, phenomenological studies, narrative research and case studies will be considered for inclusion. The included literature will be ordered in tables that describe the study characteristics and key findings. The results will be synthesised narratively.

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8 Appendices

8.1 Appendix A

Table 4 Search strategy – PubMed (MEDLINE)

Group	Query	
Population	1	Coronary[tiab]
	2	CAD[tiab]
	3	(1 OR 2) AND (obstruction[tiab] OR occlusion[tiab] OR occluded[tiab] OR stenosis[tiab] OR stenoses[tiab] OR lesion[tiab] OR "syndrome X"[tiab] OR microvascular disease*[tiab])
	4	"Coronary artery disease*"[tw]
	5	"Stable coronary disease*"[tiab]
	6	"tandem lesion*"[tiab] OR "bifurcation lesion*"[tiab] OR "atherosclerotic lesion*"[tiab] OR "coronary artery lesion*"[tiab]
	7	"Single vessel disease"[tiab]
	8	"Multivessel disease"[tiab]
	9	"Stable coronary artery disease*"[tiab]
	10	"Stable ischemic heart disease*"[tiab]
	11	"Chronic ischemic heart disease*"[tw]
	12	"Coronary heart disease*"[tw]
	13	"Atherosclerotic heart disease*"[tiab]
	14	"Nonobstructive coronary artery disease*"[tiab]
	15	"Obstructive coronary artery disease*"[tiab]
	16	Atherosclero*[tw]
	17	"Cardiovascular disease*"[tw]
	18	"chronic coronary syndrome*"[tiab]
	19	"stable angina"[tw]
	20	"after myocardial infarction*"[tiab]
	21	after[tiab] AND "anterior myocardial infarction*"[tiab]
	22	after[tiab] AND "posterior myocardial infarction*"[tiab]
	23	"Myocardial ischemia*"[tiab]
	24	"myocardial ischaemia*"[tiab]
	25	"Stable ischaemic heart disease*"[tiab]
	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**
Intervention	27	PTCA[tiab]
	28	CABG[tiab]
	29	PCI[tiab]
	30	"Coronary intervention*"[tw]
	31	"Percutaneous coronary intervention*"[tw]
	32	"Percutaneous transluminal coronary angioplasty"[tiab]
	33	"Percutaneous coronary angioplasty"[tiab]
	34	Angioplast*[tw]
	35	"Multivessel angioplasty*"[tiab]

Group	Query	
	36	"Artery angioplasty*"[tiab]
	37	"coronary angioplasty*"[tiab]
	38	Balloon angioplasty*[tiab]
	39	"Myocardial revascularisation*"[tw]
	40	"Myocardial revascularisation*"[tw]
	41	"Artery bypass grafting*"[tw]
	42	"Coronary artery bypass*"[tw]
	43	"Coronary artery bypass graft*"[tw]
	44	Angiograph*[tw]
	45	Coronary[TW] AND (START[ti] OR TOSCA[ti] OR RAVEL[ti] OR WIDEST[ti] OR ELUTES[ti] OR APPLAUSE[ti] OR TAXUS [ti] OR SIRIUS[ti] OR SCANDSTENT[ti] OR DELIVER[ti] OR SWISSI[ti] OR RITA[ti] OR GISSOC[ti] OR DESTINI[ti] OR SISCA[ti] OR LASMAL[ti] OR OCBAS[ti] OR C-SIRIUS[ti] OR ESIRIUS[ti] OR GISSOC[ti] OR PRISON[ti] OR BENESTENT[ti] OR DEBATE[ti] OR TOAT[ti] OR STOP[ti] OR ADVANCE[ti] OR SARECCO[ti] OR SICCO[ti] OR MAJIC[ti] OR Compare-Acute[ti] OR HAMBRECHT[ti] OR COURAGE[ti] OR "BARI 2D"[ti] OR "FAME 2"[ti] OR DANAMI-3-PRIMULTI[ti] OR OAT[ti] OR DECOPI[ti] OR JSAP[ti] OR ISCHEMIA[ti] OR EXACT[ti] OR AWESOME[ti])
	46	"drug-eluting stents"[tw]
	47	"coronary stent*"[tiab]
	48	"expandable stent*"[tiab]
	49	"*coated stent*"[tiab]
	50	"*eluting stent*"[tiab]
	51	"*encapsulated stent*"[tiab]
	52	"off pump bypass*"[tiab]
	53	"Bare metal stent*"[tiab]
	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**
Comparator	55	"Optimal medical therap*"[tw]
	56	"Optimal medical treatment*"[tw]
	57	"Medical therap*"[tw]
	58	"Medical treatment*"[tw]
	59	OMT[tiab]
	60	"Lipid-lowering therap*"[tiab]
	61	"Anti-ischemic drug*"[tiab]
	62	Statin*[tw]
	63	**55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62**
Language	64	English[la]
	65	French[la]
	66	German[la]
	67	Italian[la]
	68	**64 OR 65 OR 66 OR 67**
Limits	69	Animals[mh]
	70	Humans[mh]
	71	**69 NOT (69 AND 70)**
	72	Editorial[pt]

Group	Query	
	73	Letter[pt]
	74	News[pt]
	75	Congress[pt]
	76	**72 OR 73 OR 74 OR 75**
Combined search string	**77**	**(26 AND 54 AND 63 AND 68) NOT 71 NOT 76**

Table 5 Search strategy – INAHTA Database

Group	Query	
Population	1	"CCS"
	2	IHD
	3	"Ischemic heart disease"
	4	"Ischaemic heart disease"
	5	"Coronary artery disease"
	6	Atherosclerosis
Intervention	7	CABG
	8	Coronary AND bypass
	9	PCI
	10	"Percutaneous coronary intervention"
Combined search string	**11**	**(1 OR 2 OR 3 OR 4 OR 5 OR 6) AND (7 OR 8 OR 9 OR 10)**

Table 6 Search strategy – International Clinical Trials Registry Platform

Group	Query	
Population	1	CCS
	2	chronic coronary syndrome
	3	chronic ischaemic heart disease chronic
	4	chronic ischemic heart disease
	5	stable ischaemic heart disease
	6	stable ischemic heart disease
	7	stable atherosclerosis
Intervention	8	CABG
	9	coronary artery bypass graft
	10	PCI
	11	PTCA
	12	coronary angioplasty
	13	revascularisation
	14	revascularisation
Population AND Intervention	**15**	**(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7) AND (8 OR 9 OR 19 OR 11 OR 12 OR 13 OR 14)**

Table 7 Search strategy – EconLit (EBSCO)

Group	Query	
Population	1	CCS
	2	“coronary artery disease”
	3	“heart disease”
	4	Atherosclerosis
	5	Coronary
Intervention	6	Coronary angioplasty
	7	CABG
	8	Percutaneous coronary intervention
	9	PTCA
Combined search string	**10**	**(1 OR 2 OR 3 OR 4 OR 5) AND (6 OR 7 OR 8 OR 9)**

Table 8 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 für Kardiologie]	www.swisscardio.ch
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.