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Section Health Technology Assessment

Health Technology Assessment Short Report

Title	Dual Antiplatelet Therapy following Percutaneous Coronary Intervention
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Technology	Dual Antiplatelet Therapy
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Type of Technology	Pharmaceutical

Executive Summary

Policy Question

The Swiss Federal Department of Home Affairs commissioned the Federal Office of Public health (FOPH) to evaluate the evidence pertaining to the comparative clinical efficacy and safety of six to 12 months dual antiplatelet therapy (DAPT) versus extended DAPT (>12 months), following percutaneous coronary intervention (PCI) with stent insertion in coronary artery disease (CAD) patients and various subpopulations. To address this question the FOPH summarised the findings of a recent health technology assessment (HTA) report published by the Canadian Agency for Drugs and Technologies in Health that addressed the same research question. An additional research question in the Canadian report regarded an economic evaluation of the two treatment variants. A short summary of the economic analysis is also presented, be it without contextualisation of the findings in the Swiss clinical practice and reimbursement environment.

Clinical Findings

Extending DAPT beyond 12 months after PCI was shown to be associated with a reduced risk of myocardial infarction (MI) and of probable and definite stent thrombosis in CAD patients, when compared with standard-duration DAPT (six to 12 months). At the same time, extending DAPT beyond 12 months was associated with an increased risk of bleeding. No significant differences were found in the risk of all-cause or cardiovascular death, stroke, urgent target revascularisation, major adverse cardiovascular and cerebrovascular event, or gastrointestinal bleeding between extended DAPT and standard-duration DAPT. Within the CAD patient population, patients with a previous MI, acute coronary syndrome, no diabetes or those younger than 75 years seemed to benefit the most from extending DAPT beyond 12 months following PCI with stenting.

Economic Evaluation

From an economic perspective extending DAPT beyond the initial six to 12 months after PCI showed to be slightly dominant with a small incremental benefit of 0.0160 quality of life years (QALY) and small savings of 707 Canadian dollars. However, the vast majority of the modest benefit was accrued in the post-extended DAPT phase of the model. These findings should be interpreted with caution given the high degree of uncertainty of the data during this post-extended phase.

Discussion

The CADTH HTA was conducted according to standardised procedures in a sound and reproducible manner. The clinical findings were extracted from a large body of evidence of primarily high quality.

The patient selection criteria applied in the trials excluded all patients with increased bleeding risk and those with increased risk of ischaemic events. This preselection of CAD patients should be considered when extrapolating the findings to the daily practice situation. In fact, patients with increased risk of ischaemic events may benefit the most from extended DAPT. Further research

focussed on this patient population may facilitate defining definitive patient selection criteria for extended DAPT beyond 12 months.

CAD patients selected for the trials received a BMS or a first-, second- or third-generation DES. Subgroup analyses distinguishing bare metal stent- and drug-eluting stent-treated patients were conducted. However, no subgroup analyses were conducted distinguishing first-, second- and third-generation DES-treated patients. This is a limitation of the Canadian report as the adverse event rates associated with the type of DES stent have decreased as stent technology evolved.

Conclusion

Extending DAPT duration beyond the in Switzerland common six to 12 months DAPT was shown to benefit a selected group of CAD patients after PCI. This prolongation of DAPT may prevent serious complications such as MI and stent thrombosis. Unrestricted reimbursement of DAPT for these patients seems to be justified from a clinical perspective. From a health economic perspective, extending DAPT beyond 12 months may prove to be cost-effective through prevention of serious cardiovascular and cerebrovascular events. Prior to evaluating the economic effect of these events in selected patients in Switzerland, follow-up studies are needed to evaluate the occurrence of such severe events in the post-extended DAPT phase.

Zusammenfassung

Grundsatzfrage

Das Eidgenössische Departement des Innern (EDI) hat das Bundesamt für Gesundheit (BAG) beauftragt, die Evidenz zur vergleichenden klinischen Wirksamkeit und Sicherheit der dualen thrombozytenaggregationshemmenden Therapie (DTAHT über sechs bis 12 Monate gegenüber der erweiterten DTAHT (>12 Monate) nach perkutaner Koronarintervention (PKI) mit Stenteinlage bei Patienten mit koronarer Herzkrankheit (KHK) und in verschiedenen Subpopulationen zu evaluieren. Hierfür hat das BAG die Ergebnisse eines von der Canadian Agency for Drugs and Technologies in Health (CADTH) veröffentlichten Health Technology Assessment (HTA-) Berichts, der sich mit derselben Forschungsfrage befasste, zusammengefasst. Eine weitere Forschungsfrage im kanadischen Bericht bezog sich auf eine ökonomische Beurteilung der beiden Behandlungsvarianten. So wird auch eine kurze Zusammenfassung der ökonomischen Analyse präsentiert, auch wenn hierbei die Ergebnisse nicht in den Kontext der schweizerischen klinischen Praxis und Rückvergütungssituation gesetzt werden.

Klinische Beurteilung

Es wurde aufgezeigt, dass eine Verlängerung der DTAHT über 12 Monate nach der PKI hinaus im Vergleich zu einer DTAHT mit Standarddauer (sechs bis 12 Monate) mit einem verringerten Risiko eines Myokardinfarkts (MI) und einer wahrscheinlichen und definitiven Stentthrombose bei KHK-Patienten einherging. Gleichzeitig stand die Verlängerung der DTAHT über 12 Monate hinaus im Zusammenhang mit einem erhöhten Blutungsrisiko. Zwischen der verlängerten DTAHT und der DTAHT mit Standarddauer wurden keine signifikanten Unterschiede hinsichtlich der

Gesamtmortalität oder des Risikos von kardiovaskulärem Tod, Schlaganfall, dringender Revaskularisation des Zielgefässes, schwerwiegenden unerwünschten kardiovaskulären und zerebrovaskulären Ereignissen oder gastrointestinalen Blutungen festgestellt. Innerhalb der KHK-Patientenpopulation schienen Patienten mit einem vorangegangenen MI, akutem Koronarsyndrom, ohne Diabetes oder im Alter von unter 75 Jahren am meisten von einer Verlängerung der DTAHT über 12 Monate nach der PKI mit Stenting hinaus zu profitieren.

Ökonomische Beurteilung

Aus ökonomischer Perspektive war die Verlängerung des DTAHT über die ersten sechs bis 12 Monate nach der PKI hinaus leicht vorteilhafter und bot einen kleinen inkrementellen Nutzen von 0,0160 qualitätskorrigierten Lebensjahren (QALY) und geringfügigen Einsparungen in Höhe von 707 kanadischen Dollar. Der überwiegende Teil des mässigen Nutzens wurde jedoch nach der DTAHT-Verlängerungsphase des Modells verzeichnet. Diese Ergebnisse sollten angesichts des hohen Unsicherheitsgrades der Daten in dieser Phase nach der Verlängerung mit Vorsicht interpretiert werden.

Diskussion

Der HTA der CADTH wurde nach standardisierten Verfahren auf eine solide und reproduzierbare Weise durchgeführt. Die klinischen Befunde wurden aus einer grossen Anzahl von überwiegend hochwertigen Daten extrahiert.

Die Patientenauswahlkriterien, die in den Studien zur Anwendung gekommen sind, schlossen alle Patienten mit erhöhtem Blutungsrisiko sowie mit erhöhtem Risiko für ischämische Ereignisse aus. Diese Vorauswahl bei den KHK-Patienten sollte bei der Extrapolation der Befunde auf die Situation in der täglichen Praxis berücksichtigt werden. Es könnte nämlich sein, dass Patienten mit einem erhöhten Risiko für ischämische Ereignisse am meisten von einer verlängerten DTAHT profitieren. Weitere, auf diese Patientenpopulation fokussierte Forschungsarbeiten könnten die Festlegung definitiver Auswahlkriterien für Patienten, bei denen eine über 12 Monate hinaus verlängerte DTAHT zur Anwendung kommen soll, vereinfachen.

Die für die Studien ausgewählten KHK-Patienten erhielten einen unbeschichteten Metallstent (UMS) oder einen medikamentösbeschichteten Stent (MBS) der ersten, zweiten oder dritten Generation. Es wurden Subgruppenanalysen durchgeführt, bei denen zwischen Patienten, die mit UMS und solchen, die mit MBS behandelt wurden, unterschieden wurde. Subgruppenanalysen, bei denen zwischen Patienten, die mit MBS der ersten, zweiten oder dritten Generation unterschieden wurde, fanden jedoch nicht statt. Dies stellt eine Einschränkung des kanadischen Berichts dar, da die Raten unerwünschter Ereignisse im Zusammenhang mit der Art des MBS-Stents mit der Entwicklung der Stenttechnologie zurückgegangen sind.

Schlussfolgerung

Die Verlängerung der DTAHT-Dauer über die in der Schweiz übliche Dauer von sechs bis 12 Monaten

hinaus hat sich bei einer ausgewählten Gruppe von KHK-Patienten nach der PKI als vorteilhaft erwiesen. Durch diese Verlängerung der DTAHT können schwerwiegende Komplikationen wie MI und Stentthrombose verhindert werden. Aus klinischer Perspektive scheint die uneingeschränkte Erstattung der DTAHT für diese Patienten gerechtfertigt zu sein. Aus gesundheitsökonomischer Perspektive könnte sich die Verlängerung der DTAHT-Dauer über 12 Monate hinaus aufgrund der Prävention schwerwiegender kardiovaskulärer und zerebrovaskulärer Ereignisse als kosteneffektiv erweisen. Vor der Beurteilung der ökonomischen Auswirkung dieser Ereignisse bei ausgewählten Patienten in der Schweiz müssen Folgestudien durchgeführt werden, in denen das Auftreten solcher schwerwiegenden Ereignisse nach der DTAHT-Verlängerungsphase beurteilt wird.

Synthèse

Question politique

Le Département fédéral de l'intérieur suisse a chargé l'Office fédéral de la santé publique (OFSP) d'évaluer les preuves relatives à l'efficacité et à la sécurité cliniques comparatives d'une double antiagrégation plaquettaire (DAPT) de six à 12 mois par rapport à une DAPT prolongée (>12 mois), après une intervention coronarienne percutanée (ICP) avec pose de stent chez des patients souffrant de coronaropathie et dans diverses sous-populations. Pour répondre à cette question, l'OFSP a résumé les conclusions d'un rapport d'évaluation des technologies de la santé (ETS) publié par l'Agence canadienne des médicaments et des technologies de la santé, qui portait sur la même question de recherche. Une question de recherche supplémentaire dans le rapport canadien portait sur une évaluation économique des deux variantes de traitement. Un bref résumé de l'analyse économique est également présenté, mais sans contextualisation des résultats dans le contexte de la pratique clinique et du remboursement en Suisse.

Résultats cliniques

La prolongation de la DAPT au-delà de 12 mois après l'ICP s'est révélée associée à un risque réduit d'infarctus du myocarde (IM) et de thrombose de stent probable et certaine chez les patients atteints de coronaropathie, par rapport à la DAPT de durée standard (six à 12 mois). En même temps, la prolongation de la DAPT au-delà de 12 mois a été associée à un risque accru d'hémorragie. Aucune différence significative n'a été constatée entre la DAPT prolongée et la DAPT de durée standard en ce qui concerne le risque de décès toutes causes confondues ou cardiovasculaires, d'accident vasculaire cérébral, de revascularisation urgente de la cible, d'événement cardiovasculaire et cérébrovasculaire indésirable majeur ou d'hémorragie gastro-intestinale. Au sein de la population des patients atteints de coronaropathie, les patients ayant déjà souffert d'un infarctus, d'un syndrome coronarien aigu, ne souffrant pas de diabète ou âgés de moins de 75 ans semblent être ceux qui bénéficient le plus de la prolongation de la DAPT au-delà de 12 mois après une ICP avec pose de stent.

Évaluation économique

D'un point de vue économique, l'extension de la DAPT au-delà des six à 12 mois initiaux après l'ICP s'est avérée légèrement plus profitable, avec un léger avantage supplémentaire de 0,0160 année de qualité de vie (QALY) et de petites économies de 707 dollars canadiens. Cependant, la grande

majorité de ce modeste bénéfice a été accumulé dans la phase DAPT du modèle après sa prolongation. Ces résultats doivent être interprétés avec prudence étant donné le haut degré d'incertitude des données pendant cette phase après la prolongation.

Discussion

L'ETS de l'ACMTS a été réalisée selon des procédures normalisées, de manière solide et reproductible. Les résultats cliniques ont été extraits d'un grand nombre de preuves, principalement de haute qualité.

Les critères de sélection des patients appliqués dans les essais ont exclu tous les patients présentant un risque accru d'hémorragie et ceux présentant un risque accru d'événements ischémiques. Cette présélection des patients atteints de coronaropathie doit être prise en compte lors de l'extrapolation des résultats à la situation de la pratique quotidienne. En fait, ce sont les patients présentant un risque accru d'événements ischémiques qui pourraient bénéficier le plus d'une DAPT prolongée. Des recherches supplémentaires axées sur cette population de patients pourraient faciliter la définition de critères définitifs de sélection des patients pour la prolongation de la DAPT au-delà de 12 mois.

Les patients atteints de coronaropathie sélectionnés pour les essais ont reçu un stent métallique nu ou un stent à élution médicamenteuse de première, deuxième ou troisième génération. Des analyses de sous-groupes distinguant les patients traités avec un stent en métal nu et un stent à élution médicamenteuse ont été effectuées. Cependant, aucune analyse de sous-groupe n'a été menée pour distinguer les patients traités par le stent à élution médicamenteuse de première, deuxième et troisième génération. Cela constitue une limite du rapport canadien car les taux d'événements indésirables associés au type de stent à élution médicamenteuse ont diminué au fur et à mesure de l'évolution de la technologie des stents.

Conclusion

L'extension de la durée de la DAPT au-delà de la durée habituelle de six à 12 mois en Suisse s'est avérée bénéfique pour un groupe sélectionné de patients atteints de coronaropathie après une ICP. Cette prolongation de la DAPT peut prévenir de graves complications telles que l'infarctus du myocarde et la thrombose de stent. Le remboursement sans restriction de la DAPT pour ces patients semble être justifié d'un point de vue clinique. Du point de vue de l'économie de la santé, la prolongation de la DAPT au-delà de 12 mois peut s'avérer rentable grâce à la prévention d'événements cardiovasculaires et cérébrovasculaires graves. Avant d'évaluer l'effet économique de ces événements chez des patients sélectionnés en Suisse, des études de suivi sont nécessaires pour évaluer la survenue d'événements aussi graves après la phase de DAPT prolongée.

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Abbreviations and Acronyms

ACC/AHA	American College of Cardiology/ American Heart Association
ACS	Acute Coronary Syndrome
ASA	Acetyl Salicyclic Accid
BARC	Bleeding Academic Research Consortium
BMS	Bare Metal Stent
CAD	Canadian Dollars
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence Interval
DAPT	Dual Antiplatelet Therapy
DES	Drug-Eluting Stent
DM	Diabetes Mellitus
ESC	European Association of Cardiology
GUSTO	Global Utilisation of Streptokinase and t-PA for Occluded Coronary Arteries
HTA	Health Technology Assessment
HR	Hazard Ratio
ICUR	Incremental Cost-Utility Ratio
MACCE	Major Adverse Cardiovascular and Cerebrovascular Event
MI	Myocardial Infarction
PCI	Percutaneous Coronary Intervention
PICO	Patients, Intervention, Comparator, Outcome
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RR	Relative Risk
STEMI	ST-Elevation Myocardial Infarction
TIMI	Thrombolysis in Myocardial Infarction

Objective Short Report

The objective of a short HTA report is to present a focused assessment on various aspects of a health technology. Short reports vary in methodology and presentation. This short report presents findings of a recently published Canadian HTA report entitled “Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of
Standard versus Extended Duration”. The findings of the Canadian HTA report are contextualised in the Swiss clinical practice and reimbursement policy environment.

1 Rational and Policy Question

Patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) with stenting receive routinely dual antiplatelet therapy (DAPT), a combination of aspirin and a P2Y12 inhibitor, for secondary prevention of stent thrombosis and ischaemic events such as death, heart attacks, and strokes. DAPT following PCI with stenting is typically prescribed for six to 12 months.

In the last two decades, the introduction of novel and more potent P2Y12 inhibitors [1] [2] [3, 4] combined with extending their administration [3] [4] was found to progressively reduce the risk of recurrent ischaemic coronary events [5] [6]. At the same time, longer or more potent treatments were associated with an increased risk of bleeding complications [7].

Although annual costs for drugs are registered in Switzerland, prescription behaviour among Swiss physicians regarding DAPT duration following PCI with stenting is not well recorded.
Currently P2Y12 and aspirin prescription following PCI with drug-eluting or bare metal stent insertion, is reimbursed without duration restrictions. In the last 5 years the annual overall costs for the three most prescribed P2Y12 inhibitors, clopidogrel, prasugrel und ticagrelor amounted to 26, 4 and 7 million CHF, respectively [8]. These costs are a direct result of the prescription behaviour of physicians. It was questioned whether DAPT reimbursement should be restricted or not.

A large amount of high-quality scientific data has accumulated in the recent years examining the optimal duration of DAPT for CAD patients undergoing PCI with stenting. In 2018, the Swiss Federal Department of Home Affairs commissioned the Health Technology Assessment (HTA) Agency of the Federal Office of Public Health (FOPH) to evaluate the clinical evidence pertaining to optimal DAPT duration in CAD patients following PCI with stenting. It was decided to provide a HTA short report, focussed on the available clinical evidence.

In 2019 the Canadian Agency for Drugs and Technologies in Health (CADTH) published an HTA report reviewing the clinical effectiveness and safety, as well as the cost effectiveness of shorter-duration DAPT (six to 12 months) versus longer duration (more than 12 months) in patients who have undergone PCI with stenting [9]. The HTA research question defined by the FOPH resembles the Canadian HTA agency research questions [9] [10]. To prevent duplication of work and inefficient use of resources the Swiss HTA Agency of the FOPH summarises the clinical evidence presented in the Canadian HTA report and discusses what the findings may imply for Switzerland.

In addition to evaluating the clinical evidence, the Canadians also evaluated the economic impact of extending DAPT beyond 12 months versus six to 12 months DAPT following PCI with stenting. A summary of the economic findings is also presented, without contextualisation of the findings in the Swiss clinical practice situation.

Policy Question

Should P2Y12 inhibitors in combination with aspirin be reimbursed beyond 12 months for patients who recently underwent PCI with drug-eluting or bare metal stent insertion?

2 Research Question

In order to address the policy question, the primary research question of the FOPH and the CADTH HTA report was:

Research Question 1

What is the comparative clinical efficacy and safety of six to 12 months DAPT versus 12 months or more following PCI with drug-eluting or bare metal stent insertion in:

- all post-PCI patients
- patients with a prior myocardial infarction (MI)
- patients presenting with acute coronary syndrome (ACS) at the time of PCI
- patients with diabetes
- different age subgroups
- patients who smoke

The secondary research question of the CADTH HTA report regarded the cost-effectiveness of DAPT. Although cost-effectiveness was not the primary objective of the FOPH report, a summary of the Canadian findings will be presented. The secondary research question was:

Research Question 2

What is the comparative cost-effectiveness of six to 12 months DAPT versus 12 months or more following PCI with drug-eluting or bare metal stent insertion in:

- all post-PCI patients
- patients with a prior myocardial infarction (MI)
- patients presenting with acute coronary syndrome (ACS) at the time of PCI
- patients with diabetes
- different age subgroups
- patients who smoke

3 Medical Background

Patients with coronary artery disease (CAD) exhibit a luminal narrowing in the coronary arteries causing obstruction of the blood flow to the heart, typically due to plaque formation. CAD is associated with loss of quality of life, disability and death. CAD is categorised into chronic and acute coronary syndrome.

Stable angina, unstable angina, myocardial infarction (MI) and sudden cardiac death are manifestations of the conditions [11] [12]. Although CAD mortality rates have been decreasing worldwide in the last four decades, CAD remains the leading cause of about one-third of all deaths among persons over the age of 35 years [13].

Percutaneous coronary intervention (PCI) with placement of an intracoronary stent is a non-surgical procedure used to treat luminal narrowing of the coronary arteries. The procedure involves combining coronary balloon angioplasty with stenting, which is the insertion of a permanent wire-meshed stents. The first stents, introduced in the late eighties, were made of stainless steel, the bare metal stent (BMS). One of the drawbacks of the BMS was the potential for in-stent restenosis via the development of a thick smooth muscle tissue inside the lumen. Consequently, research focused on the reduction of the risk of restenosis after stent placement. The application of anti-proliferative agents was the logical answer and stents soon evolved to become efficient local drug delivery platforms. In 1999, the first drug eluting stents (DES) was implanted. First generation DES reduced in-stent-restenosis[14–16], but were associated with increased risk of late and very late stent thrombosis [17]. Second and third generation stents have been developed since, using different polymer compositions (e.g. biodegradable polymers), distribution, and thickness, new materials for the stent platform that change their geometry and strut thickness, and expanding the selection and dosage of anti-proliferative agents [18]. The newer generation stents have reduced the risk on in-stent restenosis and late and very late stent thrombosis further [18]. Swiss cardiologists have followed the evolution in stent technology and typically use newer generation DES rather than BMS.

PCI is performed in people with an acute heart attack, but also in people with less acute forms of MI or unstable angina, where there is a high risk of further events. In people with stable angina pectoris, particularly if the symptoms are difficult to control with medication, PCI is also a valid treatment option [19].

In addition to optimising stent technology, CAD patients undergoing PCI with placement of an intracoronary stent are given dual antiplatelet therapy (DAPT), to reduce the risk of stent thrombosis and major adverse cardiovascular and cerebrovascular events (MACCEs), through inhibiting platelet activity. DAPT is a combination of aspirin (acetylsalicylic acid) and a P2Y12 inhibitor. Stent thrombosis can occur acute (within 24 hours), subacute (within 30 days), late (30 days to 1 year) or very late (≥1 year) after stent placement[20]. Following PCI with stenting, DAPT is typically prescribed for six to 12 months, depending on patient-specific ischaemic and bleeding risk profiles and type of stent [21] [22].

Both aspirin and adenosine diphosphate (ADP) P2Y12 receptor antagonists are very effective antiplatelet drugs in acute and long-term secondary prevention of ischaemic events. Clopidogrel, prasugrel and ticogrelor are the most commonly prescribed P2Y12 agents.

Since the introduction of the first P2Y12 inhibitors, newer drugs have shown to be more potent, faster in onset and their platelet aggregation inhibiting capacity was shown to be more predictable. Their

introduction enabled prolongation of their administration, which was found to progressively reduce the risk of recurrent ischaemic coronary events. Inevitable, prolonging DAPT treatment with more potent P2Y12 agents was associated with an increased risk of bleeding complications, which are associated with a higher morbidity and mortality. Finding the optimal duration of DAPT has been studied for many years, resulting in a large amount of clinical evidence [23].

4 Technology

Dual antiplatelet therapy (DAPT) is a combination of aspirin (acetylsalicylic acid) and a P2Y12 receptor inhibitor. Both drugs inhibit platelet aggregation, affecting blood clot formation.

Aspirin – a cyclooxygenase inhibitor - exerts its inhibitory effect by irreversible acetylation of a serine residue of cyclooxygenase-1 and -2, thereby blocking synthesis of prostaglandin G2 and H2, and consequently thromboxane A2 generation [24]. Thromboxane A2 is a stimulator of platelet aggregation.

P2Y12 receptors are a biological target for the treatment of thromboembolisms and other clotting disorders. The drugs clopidogrel, prasugrel, and ticagrelor are the most known P2Y12 receptor inhibitors [25]. Clopidogrel and prasugrel are prodrugs that belong to the thienopyridine family, while ticagrelor belongs to the cyclopentyl-traizolopyrimidine family. Clopidogrel and prasugrel P2Y12 receptor inhibitors exert their ADP-mediated platelet aggregation irreversible inhibiting effect after being metabolised by the hepatic cytochrome P450 enzyme system. Ticagrelor is an orally active and reversible drug that has a faster onset of action than the prodrugs clopidogrel and prasugrel [24 26].

The effects of aspirin against arterial thrombosis are satiable at low doses, i.e., 75–100 mg, and typically require a single daily administration. Loading and daily dosages of P2Y12 inhibitors vary and depend on type of P2Y12 inhibitor and patient subgroup [22].

In the last 5 years the annual costs for the three most prescribed P2Y23 inhibitors, clopidogrel, prasugrel und ticagrelor amounted to 26, 4 and 7 million CHF, respectively [8].

5 Methods - Clinical Evidence

In 2019 CADTH published a systematic review that included randomised controlled trials (RCTs) that investigated the benefits and harms associated with extended DAPT beyond 12 months [9]. The protocol for the review was developed a priori and was registered in PROSPERO (No. CRD42018082587). The protocol and review followed the methods of the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA checklist for systematic reviews [27 28].

Included were RCTs involving adult patients who received DAPT following PCI with stenting for six to 12 months compared with more than 12 months. The primary outcomes were all-cause, cardiovascular and non-cardiovascular death. Secondary outcomes were MI, stroke, stent thrombosis, urgent target

vessel revascularisation, major adverse cardiovascular events, and bleeding (major, minor, or gastrointestinal bleeding).

The FOPH summarises the methodology applied to extract the clinical evidence regarding DAPT in CAD patients following PCI with stenting, by the CADTH authors.

5.1 Literature Search Strategy

Evidence evaluated for the review was obtained primarily from searches of the MEDLINE (1946 to February 1, 2018), Embase (1974 to February 1, 2018), Cochrane Library and Pubmed (November 17, 2017) databases. The search strategy included MeSH (Medical Subject Headings) and keywords. The main search concepts were dual antiplatelet therapy (DAPT) and patients requiring PCI or stents. Methodological filters were applied to limit retrieval to randomised controlled trials (RCTs). Retrieval was limited to the human population. Retrieval was not limited by publication year or language. Conference abstracts and opinion pieces were excluded. Regular search updates were performed and search alerts were run.

5.2 Selection Criteria

Studies were selected for inclusion that met the population, intervention, comparator, and study design criteria (***Table 1***). Studies were not included or excluded on the basis of reported outcomes.

Table 1: Selection Criteria

PICO Components	Inclusion Criteria
Populations(s)	Adult patients who have undergone PCI with any type of stent and who are receiving DAPT
Intervention(s)	DAPT following PCI with stenting for an extended duration (more than 12 months). DAPT may involve any type of P2Y12 inhibitor in combination with ASA
Comparator(s)	DAPT following PCI with stenting for six to 12 months. DAPT may involve any type of P2Y12 inhibitor in combination with ASA
Outcomes	Primary outcome: death (cardiovascular, all-cause, non-cardiovascular) Secondary outcomes: bleeding (major, minor, gastrointestinal), urgent target vessel revascularisation, major adverse cardiac and cerebrovascular events, myocardial infarction, stroke, and stent thrombosis

Key: ASA, acetylsalicyclic acid; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; PICO, population, intervention, comparator, outcome

Populations and Subgroups

Adult patients who had undergone PCI with any type of stent and who received DAPT were included. If less than 85% of patients did not undergo stent implantation, studies were excluded, unless data were reported separately for patients who underwent stenting. Subgroups of interest were:

- patients with a prior MI
- patients presenting with ACS
- diabetic patients
- age subgroups: patients aged less than 75 years or aged 75 years and older
- patients who smoke

Interventions

DAPT following PCI with stenting for more than 12 months. For DAPT any type of P2Y12 inhibitor at any dose was allowed, in combination with ASA at any dose.

Comparators

DAPT following PCI with stenting for six to 12 months. For DAPT any type of P2Y12 inhibitor at any dose was allowed, in combination with ASA at any dose. Other DAPT regimens or durations were beyond the scope of the review.

Outcomes

The primary outcome was death (all-cause, cardiovascular, non-cardiovascular). The secondary outcomes included urgent target vessel revascularisation, MACCE, MI, stroke, and stent thrombosis, as well as major, minor, and gastrointestinal bleeding, as defined by the individual study protocols and/or publications. A range of MACCE and bleeding classifications and definitions were encountered. Data for MACCE and bleeding outcomes were extracted based on the definitions provided by the study authors. Data were pooled for MACCE when the components of the composite outcome were deemed sufficiently similar. Bleeding outcomes were categorised by classification type, i.e., TIMI (thrombolysis in myocardial infarction), BARC (Bleeding Academic Research Consortium) and GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries).

Data from studies that included events that occurred during the early DAPT period (zero to six months after PCI) were not pooled with data from studies that reported outcomes data from the period starting six to 12 months following PCI.

5.3 Study Selection Process

Two independent reviewers applied the eligibility criteria to each title and abstract identified in the literature search. All records deemed potentially relevant by at least one reviewer were obtained in full-text format. The eligibility criteria were applied to the full-text records by both reviewers independently, and a final decision about eligibility was made. Conflicts were resolved by consensus. The reviewers were not blinded to study authors or centre of publication prior to study selection. Study screening and assessment of eligibility was facilitated and standardised through the use of DistillerSR (Evidence Partners).

5.4 Quality Assessment

The Cochrane risk-of-bias tool (RoB) version 2.0 was applied to selected RCTs that reported at least one outcome of interest [28]. The RoB tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other issues". Each domain includes one or more specific entries in an RoB table. The tool classifies risk-of-bias as "LOW," "HIGH," or "UNCLEAR".

For each unique RCT, the quality of the original primary publication was assessed. Assessments were performed by one reviewer and verified by a second reviewer. Disagreements were resolved by consensus. Publication bias was assessed by visual inspection of funnel plots for outcomes that involved data from more than 10 studies [28].

5.5 Data Extraction

The original, primary publication for each included RCT was used for data extraction, with supplementary data obtained from companion reports and ClinicalTrials.gov records, where necessary, to address the research questions. In situations where multiple publications for a unique RCT were available the most recently adjudicated data for each outcome were extracted, with preference given to published records.

Data extraction included:

- characteristics of studies, including author, year, study design, country of study
- key baseline participant characteristics (age, sex, smoking status, diabetes, prior MI, presence of ACS at presentation, history of heart failure)
- interventions studied, including duration, type of P2Y12 inhibitor
- data related to the outcomes of interest.

5.6 Data Analysis

Data for all patients, as well as for a priori defined subgroups, was analysed by random-effects, pair-wise meta-analysis by use of RevMan (v.5.3; Cochrane Collaboration). The relative risk (RR) and 95% confidence intervals (CIs) for each outcome were determined (i.e., six to12 months of DAPT versus more than 12 months of DAPT). The number of patients randomised to each group was used as the denominator for all analyses. The predefined subgroups included patients with an implanted BMS and those with a DES, patients with a prior MI, ACS at presentation, diabetes mellitus (DM), patients younger and older than 75 years, and smoking and non-smoking patients.

Clinical heterogeneity was assessed by examining the participant characteristics of the included studies, and methodological heterogeneity by assessing the study design characteristics. Statistical heterogeneity was assessed by use of the I^2 statistic, with I^2 values above 75% considered to represent substantial heterogeneity; pooled data are not reported above this threshold. The term "significant" is used to express statistical significance; otherwise, "clinical importance" is used.

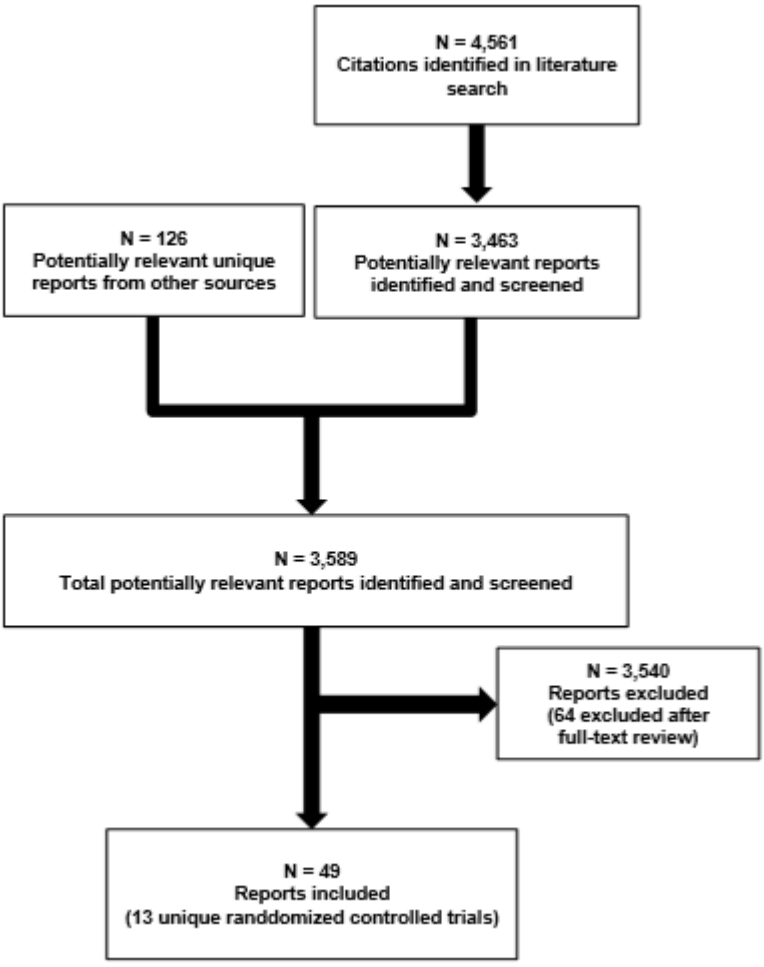
6 Findings – Clinical Evidence

The FOPH summarises the clinical findings regarding DAPT in CAD patients following PCI with stenting, presented by the CADTH authors.

6.1 Study Selection and Characteristics

The literature search identified 13 unique RCTs (***Figure 1***) [4 29–40]. Eight of the included RCTs reported data that addressed the research question [4 30 31 33 36–38 40]. The other five RCTs reported no data (ClinicalTrials.gov records) [29 34 35 39] or were available only as published protocols [32]. The evidence base of the CADTH HTA report was formed by the eight RCTs [4 30 31 33 36–38 40] that reported data. Some of the study characteristics of the selected reports are summarised below.

Figure 1: Prisma Flow Chart of Selected Reports



The included RCTs were published between 2012 and 2017, and included between 1,010 and 11,648 patients. The largest RCT was the DAPT trial, with initial outcomes data published in 2014 [4]. Seven trials were open-label, with one placebo-controlled trial. Six trials were designed to test whether extended DAPT was more effective than DAPT for a shorter duration (superiority hypothesis), while two studies tested whether extended DAPT was no worse than shorter DAPT (non-inferiority hypothesis).

The timing of randomisation relative to PCI was variable between studies. Four trials randomised patients during hospitalisation for PCI or within the first 30 days after PCI [30 31 37 38], while the remaining four trials randomised patients who completed six to 12 months of DAPT with no adverse events.

Dadjou et al. reported data starting at PCI [38], while all other studies reported data from six months after PCI. Data from the first six months following PCI with stenting include data from patients potentially at higher risk of an event. To ensure consistency across trials, data from the Dadjou et al. study [38] were excluded from the analyses. The following analyses are therefore based on data from seven trials, representing the treatment period starting six months after PCI [4 30 31 33 36 37 40].
The most frequently used P2Y12 inhibitor was clopidogrel. Four RCTs included patients taking clopidogrel (PRODIGY [31], DES-LATE [33], OPTIDUAL [36], Dadjou 2016 [38]), while four RCTs included patients taking more than one type of P2Y12 inhibitor (DAPT [4], ARCTIC-Interruption [40], ITALIC [37], NIPPON [30]). Patients in the DAPT, ARCTIC-Interruption, ITALIC and NIPPON trials received clopidogrel or prasugrel, clopidogrel or ticagrelor or clopidogrel or ticipidine. Additional information about the P2Y12 inhibitors, including dose, is provided in Appendix 1.

In the ITALIC trial by Gilard et al. (2015) ticagrelor was one of the eligible P2Y12 inhibitors. However, no participants in the 24-month DAPT group and 0.1% of participants in the six-month DAPT group received ticagrelor [37]. In addition, one large RCT (PEGASUS-TIMI 54) involving ticagrelor was identified [3]. This study did not meet the eligibility criteria and was excluded from the analysis. Together, there were insufficient data available to assess the benefits and harms of extended DAPT involving ticagrelor. However, because of its substantial size and exclusivity as only ticagrelor trial, the findings from the PESAGUS-TMI 54 trail are briefly summarised in ***Chapter 6.3.3***.
The average age of the patients was 60 years or older. Average age per study ranged from 60 to 68 years. Most of the patients were male (64% to 82%). Approximately one-third of patients in each trial had diabetes (24% to 38%) and between 23% and 61% of patients reported current smoking. Prior MI was reported in between 4% and 22% of patients. Heart failure was reported by three trials, with between 0.6% and 5% of patients reporting a history of heart failure [4 31 40].

The percentage of patients with ACS at presentation within the RCTs varied [9]. Between 0.1% and 33% of patients had ST-elevation MI (STEMI), between 2% and 23% of patients had non-STEMI, and between 9% and 39% of patients had unstable angina. Two RCTs did not report the proportion of patients with STEMI, non-STEMI, or unstable angina [38 40]. Some trials reported the percentage of complex lesions (ACC/AHA classification as Class B2 or C; 48% to 79%).

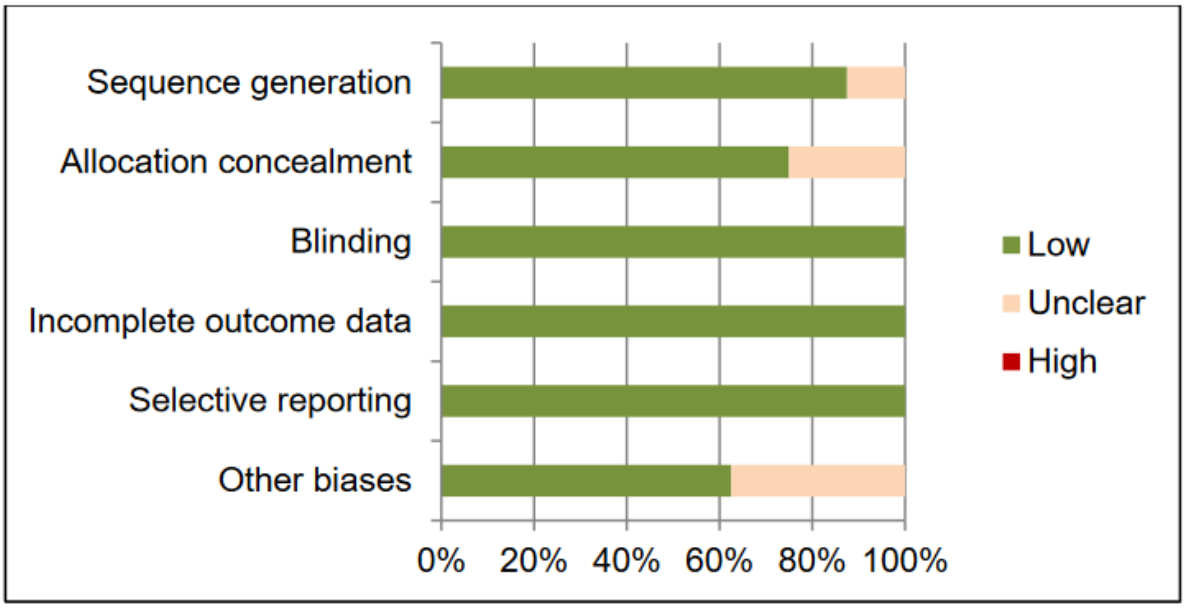
Three RCTs included patients receiving a DES or a BMS (PRODIGY [31], DAPT [4] and Dadjou 2016 [38]), while the other RCTs only included patients receiving a DES. Approximately 25% of patients in the PRODIGY trial received a BMS, while about 15% of patients in the DAPT trial included patients with a BMS [4 31]. No studies involved only patients with an implanted BMS. Commonly included DES types were everolimus-, paclitaxel-, zotarolimus-, biolimus- and sirolimus-eluting stents. Four trials [4 31 33 40] used predominantly first generation DES (paclitaxel and sirolimus eluting systems). Three trials [36–38] used

predominantly or exclusively a second generation DES (everolimus eluting systems with a durable polymer). One trial [30] used a third generation stent, a biolimus eluting stent with an absorbable polymer.

6.2 Risk of Bias

Risk of bias was assessed in all studies that reported at least one outcome of interest, using the Cochrane's RoB tool. Overall, the included RCTs were generally at low risk of bias. Most of the included RCTs were judged to be at low risk of bias for adequate sequence generation and allocation concealment (***Figure 2***), with the exception of DES-LATE and Dadjou 2016 trial, which did not provide sufficient details to permit judgment [33 38]. Although seven of the eight included RCTs were open-label, the risk of bias was judged to be low for the blinding domain for all RCTs because the outcomes were objective and unblinding would not be expected to have a large impact on the outcomes of interest. The domains "incomplete outcome data" and "selective outcome reporting" were judged to be at low risk of bias for all included RCTs. Three RCTs (ITALIC, OPTIDUAL, NIPPON) were considered to be at unclear risk of "other sources of bias", because all were terminated early [30 36 37]. Two RCTs (ITALIC, OPTIDUAL) were terminated for problems with recruitment [36 37]. The NIPPON trial was terminated after the first planned interim analysis (after 1,500 participants were followed for 18 months), because of "substantially lower overall event rates in one treatment group" and slow recruitment [30].

Figure 2: Risk of Bias Assessment of Included RCTs



6.3 Clinical Findings

6.3.1 Findings All Post-PCI Patients

Extending DAPT beyond 12 months compared with DAPT for six to 12 months was associated with a significantly reduced risk of MI (RR 0.58, 95% CI, 0.48 to 0.70) and probable or definite stent thrombosis (RR 0.38, 95% CI, 0.21 to 0.67). These benefits were associated with a significantly increased risk of

bleeding, using the GUSTO bleeding classification system (GUSTO moderate bleeding RR 1.68, 95% CI, 1.22 to 2.30). Studies using the BARC or TIMI classification systems did not confirm this increased risk. One large RCT (DAPT) reported a significant increase in non-cardiovascular death (RR 2.15, 95% CI, 1.30 to 3.55) among patients who received DAPT for more than 12 months [4]. Two smaller trials (NIPPON and OPTIDUAL) did not confirm these findings [30 36].

Table 2 summarises findings for the overall study population. A narrative description of the analyses is provided in the sections that follow.

Table 2: Summary of Findings All Post-PCI Patients

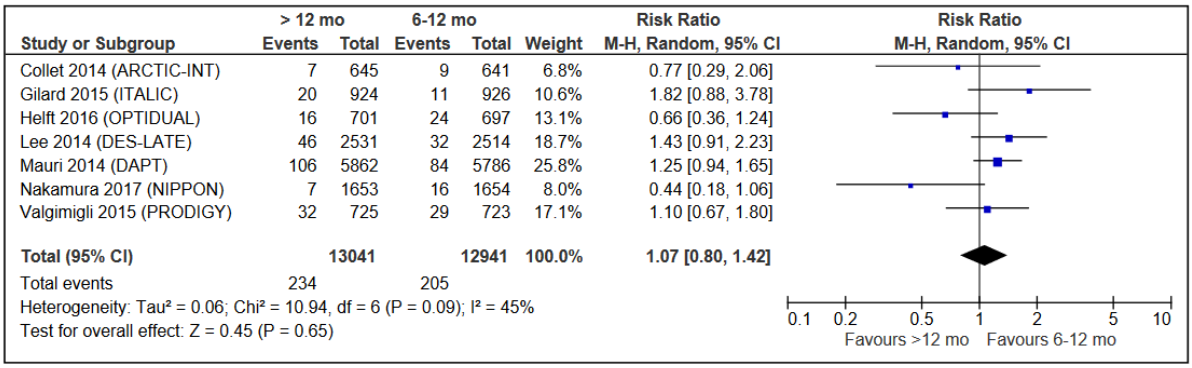
	>12 versus 6 to 12 months DAPT		
Outcome	All Patients	Patients with BMS	Patients with DES
All-cause death	↔	↔	↔
Cardiovascular death	↔	↔	↔
Non-cardiovascular death	↑/↔	NA	↑
Myocardial infarction	↓	↔	↓
Stroke	↔	↔	↔
Stent thrombosis: Definite	↔	↔	↔
Stent thrombosis: Probable of definite	↓	↔	↓
Urgent revascularisation	↔	NA	↔
MACCE	↔	↔	↔
Gastrointestinal bleeding	↔	NA	↔
TIMI major bleeding	↔	NA	↔
TIMI minor bleeding	↔	NA	↔
GUSTO moderate bleeding	↑	↔	↑
GUSTO severe bleeding	↔	↔	↔
GUSTO moderate and severe bleeding	↑	↔	↑
BARC type 2 bleeding	↔	↑	↔
BARC type 3 bleeding	↔	↑	↔
BARC type 5 bleeding	↔	↔	↔
BARC type 2, 3, 5 bleeding	↔	↑	↔

Key: ↑: risk of an event is higher with >12 months DAPT; ↓: risk of an event is lower with >12 months DAPT; ↔: no difference in event rate between6-12 months and >12 months DAPT; ↔/↓/↑: inconsistent results among studies; *: results of single trial; NA: not assessed

All-Cause Death

Seven RCTs involving 25,982 patients assessed all-cause death associated with six to 12 months of DAPT or more than 12 months of DAPT [4 30 31 36 40 41]. There was no significant difference in the risk of all-cause death between DAPT durations (RR 1.07, 95% CI, 0.80 to 1.42), with moderate heterogeneity between trials (I^2 = 45%) (***Figure 3***).

Figure 3: Relative Risk of All-Cause Death

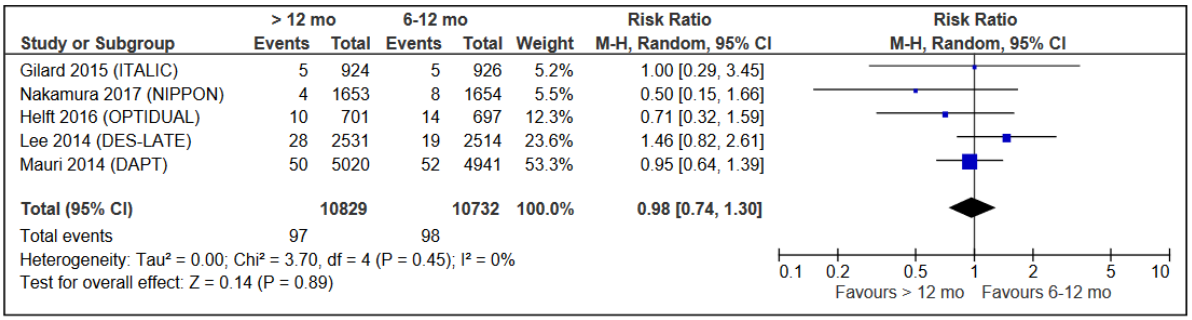


CI = confidence interval; mo = months.

Cardiovascular Death

Five RCTs involving 21,561 patients assessed cardiovascular death associated with six to 12 months of DAPT compared with more than 12 months of DAPT) [4 30 33 36 37]. There was no significant difference in the risk of cardiovascular death between DAPT durations (RR 0.98, 95% CI, 0.74 to 1.30) (***Figure 4***)

Figure 4: Relative Risk of Cardiovascular Risk

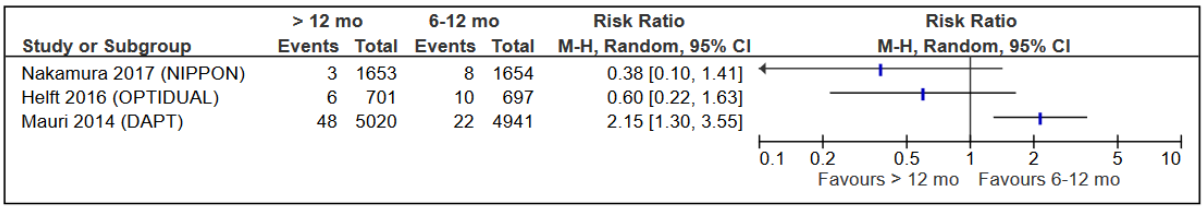


CI = confidence interval; mo = months.

Non-Cardiovascular Death

Three RCTs involving 14,666 patients assessed non-cardiovascular death associated with six to 12 months of DAPT compared with more than 12 months of DAPT [4 30 36]. No pooled analysis was performed, as there was high heterogeneity between trials (I^2 = 79%). Of note, two RCTs (NIPPON and OPTIDUAL) found no significant difference in the risk of non-cardiovascular death, while one RCT (DAPT) reported a significantly higher risk of non-cardiovascular death with DAPT for more than 12 months (RR 2.15, 1.30 to 3.55) (***Figure 5***).

Figure 5: Relative Risk of Non-Cardiovascular Risk

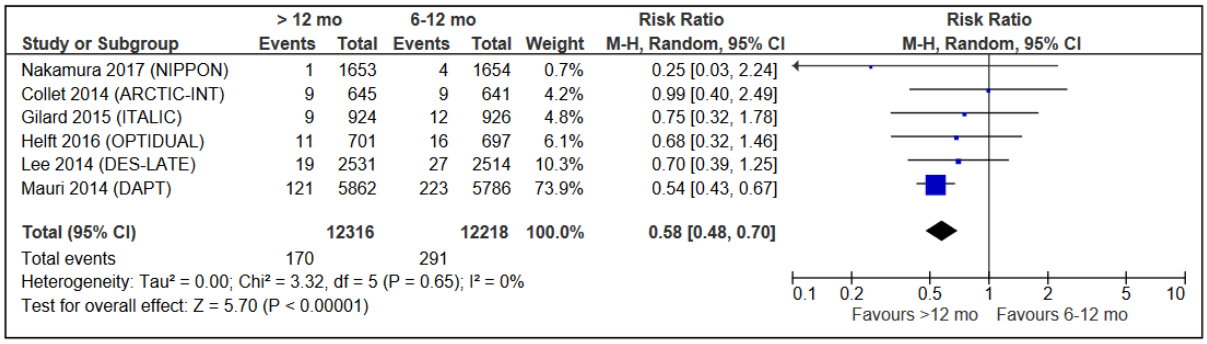


CI = confidence interval; mo = months.

Myocardial Infarction

Six RCTs involving 24,534 patients assessed MI associated with six to 12 months of DAPT compared with more than 12 months of DAPT [4 30 33 36 37 40]. Patients who received extended DAPT were at lower risk of MI compared with those who received DAPT for six to 12 months (RR 0.58, 95% CI, 0.48 to 0.70) (***Figure 6***).

Figure 6: Relative Risk of Myocardial Infarction

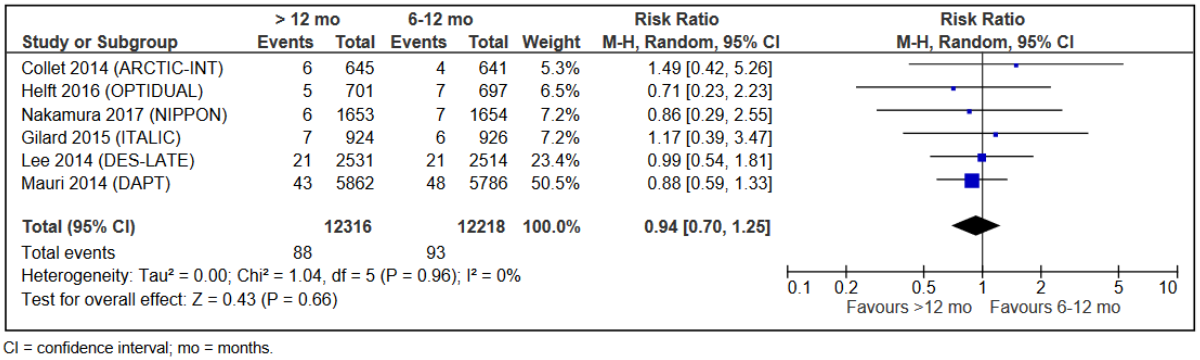


CI = confidence interval; mo = months.

Stroke

Six RCTs involving 24,534 patients assessed stroke associated with six to 12 months of DAPT compared with more than 12 months of DAPT [4 30 33 36 37 40]. There was no significant difference in the risk of stroke between DAPT durations (RR 0.94, 95% CI, 0.70 to 1.25) (***Figure 7***).

Figure 7: Relative Risk of Stroke



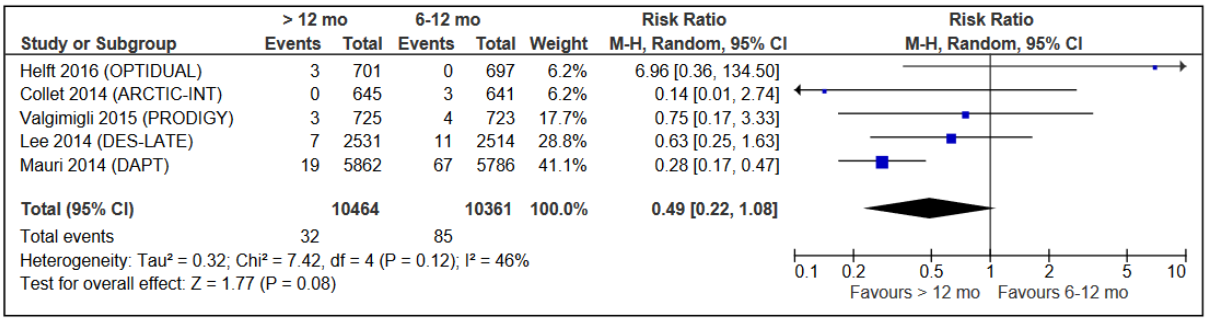
CI = confidence interval; mo = months.

Stent Thrombosis

Definite Stent Thrombosis

Five RCTs involving 20,825 patients assessed definite stent thrombosis associated with six to 12 months of DAPT compared with more than 12 months of DAPT [4 30 33 36 40]. There was no statistically significant difference in the risk of definite stent thrombosis between DAPT durations (RR 0.49, 95% CI, 0.22 to 1.08), with moderate heterogeneity between trials (I^2 = 46%) (***Figure 8***). Although this result did not reach statistical significance, there may be a protective effect of DAPT for longer than 12 months, as observed in the DAPT trial.

Figure 8: Relative Risk of Definite Stent Thrombosis

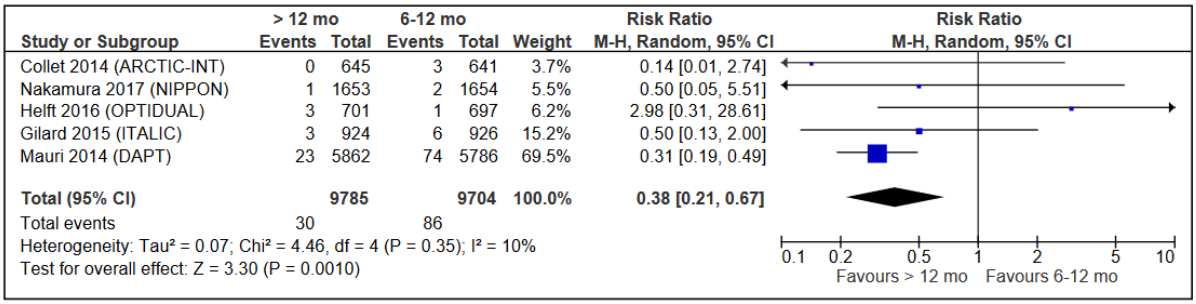


CI = confidence interval; mo = months.

Definite or Probable Stent Thrombosis

Five RCTs involving 19,489 patients assessed probable or definite stent thrombosis associated with six to 12 months of DAPT compared with more than 12 months of DAPT [4 30 36 37 40]. Patients who received extended DAPT were at lower risk of probable or stent thrombosis compared with those who received DAPT for six to 12 months (RR 0.38, 95% CI, 0.21 to 0.67), with low heterogeneity between trials (I^2 = 10%) (***Figure 9***).

Figure 9: Relative Risk of Definite or Probable Stent Thrombosis

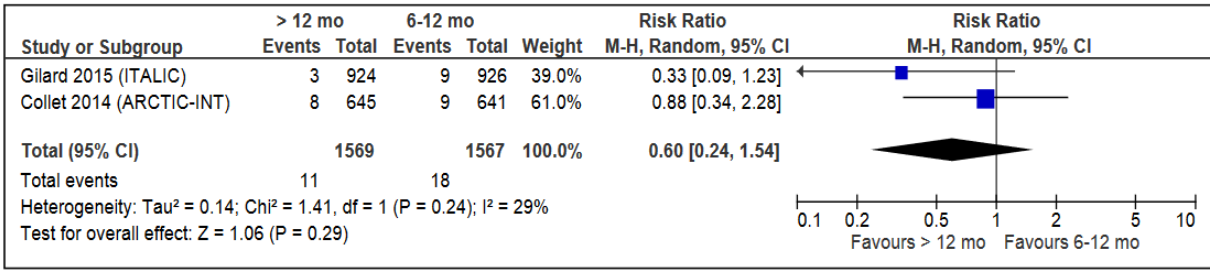


CI = confidence interval; mo = months.

Urgent Revascularisation

Two RCTs involving 3,136 patients assessed urgent revascularisation associated with six to 12 months of DAPT compared with more than 12 months of DAPT [37 40]. There was no significant difference in the risk of urgent revascularisation between DAPT durations (RR 0.60, 95% CI, 0.24 to 1.54), with moderate heterogeneity between trials (I^2 = 29%) (***Figure 10***).

Figure 10: Relative Risk of Urgent Revascularisation

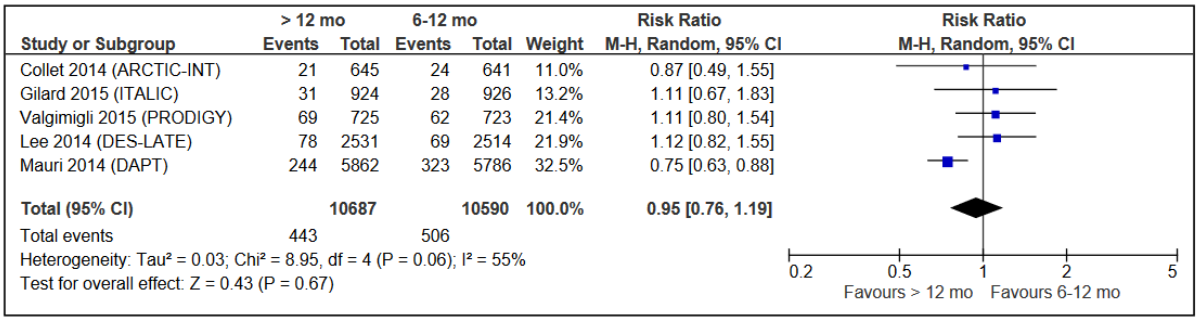


CI = confidence interval; mo = months.

MACCE

All of the included RCTs assessed the occurrence of MACCE during the treatment period, but there was wide variation in components of the composite outcome across trials. In order to ensure consistency, only data from trials that reported a composite consisting of all-cause death, MI, or stroke were pooled. This regarded five RCTs [4 31 33 37 40] that included 21,277 patients. There was no significant difference in the risk of MACCE between DAPT durations (RR 0.95, 95% CI, 0.76 to 1.19), with moderate heterogeneity between trials (I^2 = 55%) (***Figure 11***). Two additional RCTs reported MACCE by use of an alternative definition that included major bleeding, with no significant difference in the risk of an event between DAPT for six to 12 months or DAPT more than 12 months [30 36].

Figure 11: Relative Risk of MACCE



CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular event; mo = months.

Gastrointestinal Bleeding

Gastrointestinal bleeding was reported by one RCT, with no significant difference in risk between patients who received DAPT for six or 18 months (RR 0.89, 95% CI, 0.34 to 2.30; P = 0.81) [30].

Major Bleeding

A variety of bleeding classification systems was used among the included trials to assess bleeding severity, including GUSTO, BARC, TIMI, REPLACE, STEEPLE and ISTH (***Table 3***). The TIMI classification system was most commonly used among the included trials.

Table 3: Bleeding Classification Systems Used by the Included RCTs

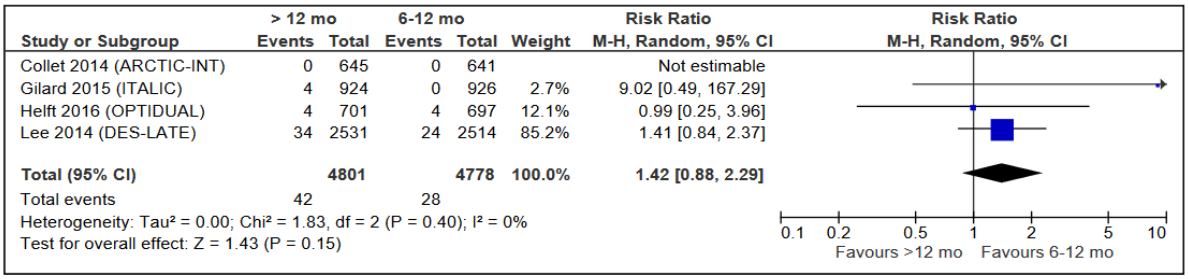
Trial	Bleeding Classification System
DAPT [4]	GUSTO, BARC

PRODIGY [31]	TIMI,BARC
ARCTIC-INT [40]	TIMI, STEEPLE
ITALIC [37]	TIMI
OPTIDUAL [36]	TIMI, BARC, GUSTO, ISTH
NIPPON [30]	BARC, RAPLACE
DEA-LATE [33]	TIMI

TIMI Major Bleeding

TIMI major bleeds were reported in four RCTs involving 9,579 patients [33 36 37 40]. Among RCTs that assessed TIMI major bleeding, there was no significant difference in the risk of TIMI major bleeding between DAPT durations (RR 1.42, 95% CI, 0.88 to 2.29) (***Figure 11***).

Figure 12: Relative Risk of TIMI Major Bleeding

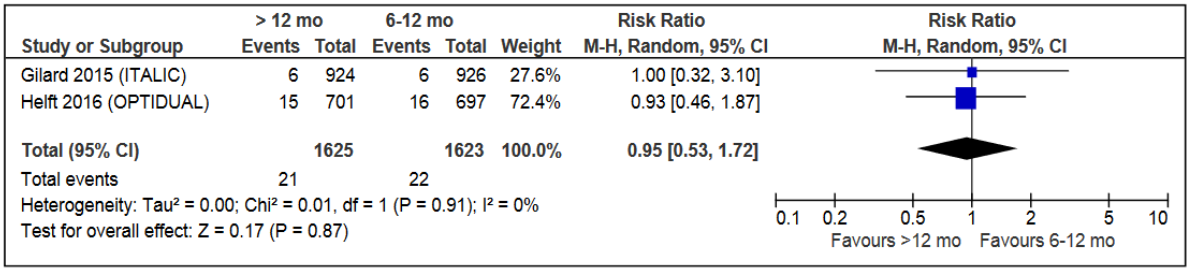


CI = confidence interval; mo = months; TIMI = thrombolysis in myocardial infarction.

TIMI Minor Bleeding

TIMI minor bleeds were reported in two RCTs involving 3,248 patients. There was no significant difference in the risk of TIMI minor bleeding between DAPT durations (RR 0.95, 95% CI, 0.53 to 1.72) (***Figure 13***) [36 37].

Figure 13: Relative Risk of TIMI Minor Bleeding



CI = confidence interval; mo = months; TIMI = thrombolysis in myocardial infarction.

Alternative Bleeding Classification Systems

Bleeding severity was also assessed by use of alternative classification systems [4 30 31 36 40]. GUSTO moderate bleeding (RR 1.68, 95% CI, 1.22, 2.30) and GUSTO moderate and severe bleeding (RR 1.57, 95% CI, 1.17, 2.11) [4 36] showed a significant difference in risk between DAPT for more than 12 months

and DAPT for six to 12 months (***Table 2***). Results from the DAPT trial suggest that there is a trend toward increased major bleeding with extended DAPT [4]. The other studies did not show any significant difference in risk of bleeding events between DAPT durations.

6.3.2 Results Subgroups Analyses

Following is a summary of subgroup analyses that showed statistically significant differences between study groups. For a complete report of all subgroup analyses, see the CADTH full report [9].

Patients with an Implanted BMS

Two RCTs involved 2,179 patients with an implanted BMS (PRODIGY and DAPT trials) or DES [4 31]. Approximately 25% of patients in the PRODIGY trial received a BMS, whereas approximately 15% of patients in the DAPT trial included patients with a BMS. These RCTs each reported data separately for patients with a BMS and form the evidence base for this subgroup (***Table 2***).

Major and Minor Bleeding

Among patients in the DAPT trial with an implanted BMS, there was a significantly higher risk of BARC type 2 bleeding (RR 3.15, 95% CI, 1.35 to 7.34), type 3 bleeding (RR 2.68, 95% CI, 1.05 to 6.81), and type 2, 3, 5 bleeding (RR 2.72, 95% CI, 1.49 to 4.99) among patients who received DAPT for more than 12 months compared with those who received DAPT for six to 12 months.

Patients with an Implanted Drug-Eluting Stent

Of the included RCTS, five involved only patients with an implanted drug-eluting stent (DES) [30 33 36 37 40]. Two additional RCTs provided subgroup data for patients with a DES [4 31]. These seven RCTs form the evidence basis to address this subgroup (***Table 2***).

Myocardial Infarction

Six RCTs involving 22,847 patients with a DES assessed MI [4 30 33 36 37 40]. Among those with an implanted DES, DAPT for more than 12 months was associated with a lower risk of MI compared with DAPT for six to 12 months (RR 0.55, 95% CI, 0.45 to 0.67).

Definite or Probable Stent Thrombosis

Five RCTs involving 17,802 patients with a DES assessed definite or probable stent thrombosis [4 30 36 37 40]. Among those with an implanted DES, DAPT for more than 12 months was associated with a lower risk of definite or probable stent thrombosis compared with DAPT for six to 12 months (RR 0.38, 95% CI, 0.20 to 0.73).

Major and Minor Bleeding

Two RCTs involving 13,046 patients with a DES assessed a statistically significant difference in risk between DAPT for more than 12 months and DAPT for six to 12 months for GUSTO moderate bleeding (RR 1.62, 95% CI, 1.16, 2.25) and moderate or severe bleeding (RR 1.53, 95% CI, 1.17, 2.00) [4 36]. No statistically significant differences in bleeding risk between the DAPT for more than 12 months and

DAPT for six to 12 months were reported in any of the other studies, using various bleeding classification systems.

Patients with a Prior MI

Two RCTs involving 5,622 patients reported outcomes among patients with a history of MI [4 37] (***Table 4***).

All-Cause Death

Two RCTs involving 5,622 patients reported all-cause death among patients with a history of MI [4 37]. Among patients with a prior MI, there was no significant difference in the risk of all-cause death between DAPT for six to 12 months or more than12 months (RR 1.04, 95% CI, 0.72 to 1.51). However, one RCT involving 6,308 patients with no history of MI reported a statistically significant increase in all-cause death among patients who received more than 12 months of DAPT following PCI (RR 1.64, 95% CI, 1.08 to 2.48) [4].

Myocardial Infarction

Two RCTs involving 5,622 patients reported the new occurrence of MI. Among patients with a prior MI, patients who received DAPT for more than 12 months were at lower risk of new MI compared with those who received six to 12 months of DAPT (RR 0.48, 95% CI, 0.36 to 0.64) [4 37]. One RCT involving 6,308 patients with no history of MI reported a significantly lower risk of new MI among patients who received more than 12 months of DAPT compared with those who received six to 12 months of DAPT (RR 0.63, 95% CI, 0.46 to 0.87) [4].

Definite of Probable Stent Thrombosis

One RCT reported a significantly lower risk of definite or probable stent thrombosis among patients with (RR 0.29, 95% CI, 0.16, 0.52) or without (RR 0.32, 95% CI, 0.15 to 0.68) prior MI [4], when receiving DAPT for more than 12 months.

MACCE

One RCT reported a significantly lower risk of MACCE (all-cause death, MI, stroke) among patients with prior MI (RR 0.67, 95% CI, 0.53 to 0.83) but no significant difference among patients with no history of MI (RR 0.87, 95% CI, 0.69, 1.10) [4], when receiving DAPT for more than 12 months.

Major and Minor Bleeding

One RCT reported a significantly higher risk of GUSTO moderate or severe bleeding (RR 1.89, 95% CI, 1.21 to 2.95; RR 1.58, 95% CI, 1.13 to 2.22), GUSTO moderate bleeding (RR 2.30, 95% CI, 1.28 to 4.11; RR 1.51, 95% CI, 1.00 to 2.26), and BARC type 2, 3, or 5 bleeding (RR 2.06, 95% CI, 1.50 to 2.82; RR 1.91, 95% CI, 1.51 to 2.42) among those who received extended DAPT compared with DAPT for six to 12 months either with or without a history of MI [4].

Patients with ACS at Presentation

In total, six RCTs reported data for patients with ACS at baseline [4 30 31 33 37 40]. The PRODIGY trial could not be pooled with the other trials, based on inconsistent period reporting [31].

Myocardial Infarction

Two RCTs involving 4,382 patients with ACS assessed MI. Among those with ACS at presentation, extended DAPT was associated with a lower risk of MI compared with DAPT for six to 12 months (RR 0.49, 95% CI, 0.29 to 0.85) [4 37] (***Table 4***).

Definite or Probable Stent Thrombosis

One RCT involving 3,576 patients with ACS assessed definite or probable stent thrombosis. Among those with ACS at presentation, those who received DAPT for more than 12 months were at a lower risk of definite or probable stent thrombosis compared with those who received DAPT for six to 12 months (RR 0.26, 95% CI, 0.12 to 0.54) [4].

MACCE

Two RCTs involving 6,639 patients with ACS assessed MACCE by use of a consistent definition (all-cause death, MI, stroke) [4 33]. The results of these trials were not pooled because of high heterogeneity (I^2 = 80%). One RCT (DAPT) reported a statistically significant decrease in MACCE among patients with ACS who received extended DAPT (RR 0.57, 95% CI, 0.43 to 0.76). The second RCT (DES-LATE) reported no significant difference in MACCE in this group (RR 1.05, 95% CI, 0.67 to 1.65).

Major and Minor Bleeding

Among patients with ACS, extended DAPT was associated with a significantly higher risk of BARC type 2, 3, or 5 bleeding (RR 2.38, 95% CI, 1.28 to 4.42); GUSTO moderate or severe bleeding (RR 4.23, 95% CI, 1.64 to 11.37); and GUSTO moderate bleeding (RR 2.07, 95% CI, 1.41 to 3.04); but no statistically significant difference in GUSTO severe bleeding.

Patients with Diabetes

Two RCTs reported outcomes among 4,076 patients with diabetes [4 37].

Major and Minor Bleeding

Among patients with diabetes, extended DAPT was associated with a significantly higher risk of BARC type 2, 3, or 5 bleeding (RR 1.59, 95% CI, 1.15 to 2.19), as well as BARC type 3 bleeding (RR 1.75, 95% CI, 1.07 to 2.86).

Table 4: Summary of Findings Patients with or without a prior MI, ACS or Diabetes

	>12 versus 6 to 12 months DAPT					
Outcome	Prior MI	No prior MI	ACS	No ASC	Diabetes	No Diabetes
All-cause death	↔	↑*	↔	NA	↔	↔*

Cardiovascular death	↔	↔	↔*	NA	↔	NA
Non-cardiovascular death	↔	↔	↔	NA	↔*	NA
Myocardial infarction	↓	↓*	↓	NA	↔	↓*
Stroke	↔	↔	NA	NA	↔*	NA
Stent thrombosis: Definite	↔	↔	NA	NA	↔*	NA
Stent thrombosis: Probable of definite	↔**	↔*	↓*	NA	↔*	↓*
Urgent revascularisation	↔	↔	↔*	NA	↔*	NA
MACCE	↓*	↔*	↔/↓	NA	↔	↔/↓*
Gastrointestinal bleeding	NA	NA	NA	NA	NA	NA
TIMI major bleeding	↔	↔	NA	NA	NA	NA
TIMI minor bleeding	↔	↔	↔*	NA	↔*	NA
GUSTO moderate bleeding	↑*	↑*	↑	NA	↔	↔↑
GUSTO severe bleeding	↔*	↔*	↔	NA	↔	↔
GUSTO moderate and severe bleeding	↑*	↑*	↑	NA	↔	↑
BARC type 2 bleeding	↔*	↔*	↔	NA	↑	↔
BARC type 3 bleeding	↔*	↔*	↔	NA	↑	↔
BARC type 5 bleeding	↔*	↔*	↔	NA	↔	↔
BARC type 2, 3, 5 bleeding	↑*	↑*	↑	NA	↑	↔

Key: ↑: risk of an event is higher with >12 months DAPT; ↓: risk of an event is lower with >12 months DAPT; ↔: no difference in event rate between6-12 months and >12 months DAPT; ↔/↓/↑: inconsistent results among studies; *: results of single trial; NA: not assessed

Age

Five RCTs reported outcomes based on age, i.e. patients aged less than 75 years or those older than 75 years [4 30 31 37 40]. One additional RCT provided risk outcomes data among those aged less than 65 years or those older than 65 years [33].

Myocardial Infarction

One RCT (DAPT) reported that there was a significantly lower risk of MI with extended DAPT among patients aged less than 75 years (HR 0.46, 95%CI 0.36 to 0.60) but not among those aged more than 75 years (HR 0.76, 95% CI, 0.38 to 1.54) [4].

Stroke

One RCT assessed the risk of stroke among 587 patients aged at least 75 years and 1,383 patients aged less than 75 years [31]. Among patients aged at least 75 years, the risk of stroke was significantly higher in those who received DAPT for more than 12 months compared with six to 12 months (RR 8.59, 95% CI, 1.08 to 68.28). Among those aged less than 75 years, there was no significant difference in risk between DAPT for more than 12 months and six to 12 months (RR 2.89, 95% CI, 0.79 to 10.64).

Probable or Definite Stent Thrombosis

One RCT (DAPT) reported that there was a significantly lower risk of definite or probable stent thrombosis among patients aged less than 75 years who received DAPT for more than 12 months (HR 0.29, 95% CI, 0.17 to 0.49) but not among those aged more than 75 years (HR 0.23, 95% CI, 0.03 to 2.06) [4].

MACCE

One RCT reported a significantly lower risk of MACCE among those aged less than 75 years who received more than 12 months of DAPT compared with six to 12 months of DAPT (HR 0.69, 95% CI, 0.57, 0.83), but not among those at least 75 years (HR 0.95, 95% CI, 0.59, 1.52) [4].

Major and Minor Bleeding

Among patients aged more than 75 years, extended DAPT was associated with a significantly higher risk of BARC type 2, 3, and 5 bleeding (RR 2.75, 95% CI, 1.29 to 5.83); BARC type 3 and 5 bleeding (RR 3.01, 95% CI, 1.10 to 8.24); and GUSTO moderate and severe bleeding (RR 5.01, 95% CI, 1.46 to 17.26). Among those aged less than 75 years, there was a significant increase in the risk of BARC type 2, 3, or 5 bleeding (RR 2.63, 95% CI, 1.33 to 5.21).

Patients who Smoke

Three RCTs reported outcomes data by smoking status [4 31 40].

Myocardial Infraction

The DAPT trial reported a significantly lower risk of MI with DAPT for more than 12 months compared with DAPT for six to 12 months among both smokers (RR 0.38, 95% CI, 0.24 to 0.60) and non-smokers (RR 0.55, 95% CI, 0.41 to 0.72) [4].

Probable and Definite Stent Thrombosis

The DAPT trial reported a significantly lower risk of definite or probable stent thrombosis with DAPT for more than 12 months compared with DAPT for six to 12 months among both smokers (RR 0.20, 95% CI, 0.09 to 0.49) and non-smokers (RR 0.36, 95% CI, 0.19 to 0.67) [4].

MACCE

The DAPT und PRODIGY trails reported MACCE using a similar definition (all-cause death, MI, stroke). Among smokers, DAPT for more than 12 months was associated with a lower risk of MACCE (RR 0.69, 95% CI, 0.52 to 0.91) compared with DAPT for six to 12 months. Among non-smokers, there was no significant difference in the risk of MACCE between DAPT durations (RR 0.87, 95% CI, 0.64 to 1.20) [4 31].

Major and Minor Bleedings

The risk of bleeding was increased among non-smokers who received DAPT for more than 12 months compared with DAPT for six to 12 months, using of either the GUSTO moderate or severe (RR 1.83, 95% CI, 1.32 to 2.52) or BARC type 2, 3, and 5 (RR 2.44, 95% CI, 1.54 to 3.87) classification [4 31]. Among smokers, there was no significant difference in the risk of bleeding between DAPT durations by use of either classification system.

Table 5: Summary of Findings Patients aged ≥ or < 75 years and Patients who smoke or not smoke

	>12 versus 6 to 12 months DAPT			
Outcome	≥ 75 years	< 75 years	Smokers	Non-Smokers
All-cause death	↔	↔*	↔	↔*
Cardiovascular death	↔	↔*	NA	NA
Non-cardiovascular death	NA	NA	NA	NA
Myocardial infarction	↔	↔*/ ↓*	↓*	↓*
Stroke	↑*	↔*	NA	NA
Stent thrombosis: Definite	↔*	↔*	NA	NA
Stent thrombosis: Probable of definite	↔*	↔*/ ↓*	↓*	↓*
Urgent revascularisation	↔*	NA	NA	NA
MACCE	↔**	↔*/ ↓*	↓*	↔

Gastrointestinal bleeding	NA	NA	NA	NA
TIMI major bleeding	NA	NA	NA	NA
TIMI minor bleeding	↔**	NA	NA	NA
GUSTO moderate bleeding	NA	NA	NA	NA
GUSTO severe bleeding	NA	NA	NA	NA
GUSTO moderate and severe bleeding	↑*	↔*	↔	↑
BARC type 2 bleeding	NA	NA	NA	NA
BARC type 3 bleeding	NA	NA	NA	NA
BARC type 5 bleeding	NA	NA	NA	NA
BARC type 2, 3, 5 bleeding	↑*	↑*	↔	↑

Key: ↑: risk of an event is higher with >12 months DAPT; ↓: risk of an event is lower with >12 months DAPT; ↔: no difference in event rate between6-12 months and >12 months DAPT; ↔/↓/↑: inconsistent results among studies; *****: results of single trial; NA: not assessed

6.3.3 Results Ticagrelor

Insufficient data was available to assess the benefits and harms of extended DAPT involving ticagrelor. The only large RC using ticagrelor as P2Y12 inihibitor was the PEGASUS-TIMI 54 trial [3]. This trial did not meet the eligibility criteria as participants were randomised to ticagrelor 60 mg or 90 mg twice daily, or placebo, one to three years after an MI (median 1.7, interquartile range 1.2 to 2.3 years). Moreover, there was uncertainty about whether all participants received tricagrelor and less than 85% of patients had undergone PCI with stenting.

Given the lack of sufficient other ticagrelor evidence, results from this RCT may be of interest to some and are summarised below.

Participants in PEGASUS-TIMI 54 were randomised to ticagrelor 60 mg or 90 mg twice daily or placebo (n = 21’162) and were followed for a median of 33 months (interquartile range 28 month to 37 months). The primary efficacy outcome was a composite of cardiovascular death, MI, or stroke. The primary safety outcome was thrombolysis in MI (TIMI) major bleeding.

Among all participants (with or without PCI), both ticagrelor 60 mg and 90 mg twice daily reduced the primary outcome compared with placebo (ticagrelor 60 mg versus placebo: HR 0.84, 95% CI, 0.74 to 0.95; ticagrelor 90 mg versus placebo: HR 0.85, 95% CI, 0.75 to 0.96).

For both doses, ticagrelor use was associated with a lower risk of MI compared with placebo (ticagrelor 60 mg versus placebo: HR 0.84, 95% CI, 0.72 to 0.98; ticagrelor 90 mg versus placebo: HR 0.81, 95% CI, 0.69 to 0.95), with no significant differences in all-cause death (ticagrelor 60 mg versus placebo: HR 0.89, 95% CI, 0.76 to 1.04; ticagrelor 90 mg versus placebo: HR 1.00, 95% CI, 0.86 to 1.16) or cardiovascular death (ticagrelor 60 mg versus placebo: HR 0.83, 95% CI, 0.68 to 1.01; ticagrelor 90 mg versus placebo: HR 0.87, 95% CI, 0.71 to 1.06). Ticagrelor 60 mg, but not 90 mg, was associated with a reduction in the risk of stroke (ticagrelor 60 mg versus placebo: HR 0.75, 95% CI, 0.57 to 0.98; ticagrelor 90 mg versus placebo HR 0.82, 95% CI, 0.63 to 1.07). The risk of TIMI major bleeding was significantly higher with both doses of ticagrelor (ticagrelor 60 mg versus placebo: HR 2.32, 95% CI, 1.68 to 3.21; ticagrelor 90 mg versus placebo HR 2.69, 95% CI, 1.96 to 3.70), as well as TIMI minor bleeding (ticagrelor 60 mg versus placebo: HR 3.31, 95% CI, 1.94 to 5.63; ticagrelor 90 mg versus placebo HR 4.15, 95% CI, 2.47 to 7.00) [3].

Among participants who had prior PCI, the risk of the primary outcome was significantly lower among those who had received ticagrelor (ticagrelor 60 mg versus placebo: HR 0.83, 95% CI, 0.72 to 0.96; ticagrelor 90 mg versus placebo HR 0.86, 95% CI, 0.74 to 0.98). The risk of TIMI major bleeding was, however, higher (ticagrelor 60 mg versus placebo: HR 2.42, 95% CI, 1.70 to 3.44; ticagrelor 90 mg versus placebo HR 2.76, 95% CI, 1.95 to 3.91) [3].

7 Methods – Economic Evaluation

The FOPH summarises the methodology applied by the CADTH authors to analyse the cost-effectiveness and budget impact of extended DAPT versus 6 to 12 months DAPT in CAD patients following stenting.

The authors conducted a cost-utility analysis, using a two-phase Markov cohort model, to address the secondary research question (***Chapter 2***). The findings of the clinical evidence evaluation (***Chapter 6***) were used to inform the clinical efficacy and safety outcomes in the model. For long-term outcomes, utilities, and costs the medical literature was used to supplement the findings. In Canada a general acceptability threshold value of 50'000 CAD per quality adjusted life year (QALY) is assumed (conversion rate on July 1st , 2018: 1 CAD = 0.73 CHF) [42].

The first cycle of the model (the extended DAPT phase) was informed by the results of effectiveness evaluation analyses (***Chapter 6***) and the end points from the studies; i.e., all-cause mortality, non-fatal MI, non-fatal stroke, probable or definite stent thrombosis, urgent revascularisation, and bleeding. The

cohort received ASA or extended DAPT according to the treatment duration of the various studies included in the effectiveness analyses (i.e., 12 to 36 months beyond the initial six to 12 months of DAPT; ***Chapter 6***). The cohort moved into the second cycle of the model (the post-extended DAPT phase) after having completed the extended DAPT cycle. This phase reflected the rest of their lives; i.e., up to 100 years of age. During this cycle all patients received ASA 62.5 mg to 125 mg per day for the rest of the time horizon. In the post-extended DAPT phase, additional health states were included to reflect the possibility of having subsequent cardiovascular events (e.g., stroke or second MI in an MI patient, MI or second stroke in stroke patients).

Primary outcomes were costs, life-years, and QALYs derived from the presence or absence of clinical events such as all-cause death, non-fatal MI, non-fatal stroke, definite or probable stent thrombosis, urgent revascularisation, and bleeds. Costs, life-years, and quality adjusted life-years (QALYs) were discounted at 1.5% per year (0% and 3% in sensitivity analyses). To account for parameter uncertainty all calculations were performed in a probabilistic sensitivity analysis, analysing 5'000 iterations.

To address the uncertainty in the post-extended DAPT phase of the model and the uncertainty related to some inputs, univariate sensitivity analyses were performed.

To complement the base-case analysis, scenario analyses were performed for the following subgroups of patients: ACS patients, patients with or without a prior MI or diabetes and patients younger and older than 75 years.

8 Findings - Economic Evaluation

Below is a summary of the findings of the economic evaluation presented, conducted by the CADTH authors comparing extended DAPT versus 6 to 12 months DAPT in CAD patients following PCI with stenting. The findings were not contextualised in the Swiss clinical practice and reimbursement environment.

8.1 Base Case Analysis

Clinical Outcomes

Only very modest differences (i.e., ± 1% or 2%) in clinical outcomes between the six- to 12-month DAPT and the extended DAPT arms were shown (***Table 6***). The largest difference was a 1.24% reduction in MI, which translated into a 0.85% reduction in death post-MI. Consequently, the life-year and QALY gains for extended DAPT were small (i.e., 0.0166 and 0.0160, respectively) (***Table 7***).

Table 6: Model Results – Clinical Outcomes

	6- to 12-Month DAPT			Extended DAPT			
Clinical Outcome	Extended DAPT Phase	Post-Extended DAPT Phase	Total	Extended DAPT Phase	Post-Extended DAPT Phase	Total	Difference (Extended DAPT: 6- to 12-month DAPT)
MI	2.32%	36.94%	39.26%	1.34%	36.68%	38.01%	–1.24%
Stroke	0.73%	13.19%	13.93%	0.70%	13.07%	13.77%	–0.16%
Urgent revascularization	1.20%	11.73%	12.94%	0.73%	11.90%	12.63%	–0.31%
Stent thrombosis	0.91%	8.93%	9.84%	0.30%	9.04%	9.34%	-0.49%
Bleeding events	1.30%	12.05%	13.35%	1.52%	12.20%	13.73%	+0.37%
All-cause death	1.55%			1.74%			+0.18%
Death post-MI		34.64%			33.78%		-0.85%
Death post-stroke		9.41%			9.30%		-0.11%
Fatal bleeding events		0.69%			0.70%		+0.01%

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

Table 7: Model Results - Life-Year and Quality-Adjusted Life-Year

	6- to 12-Month DAPT			Extended DAPT			
	Extended DAPT Phase	Post-Extended DAPT Phase	Total	Extended DAPT Phase	Post-Extended DAPT Phase	Total	Difference (Extended DAPT: 6- to 12-month DAPT)
LY	1.54	16.18	17.72	1.54	16.19	17.73	0.0166
QALY	1.23	12.41	13.64	1.23	12.42	13.65	0.0160

DAPT = dual antiplatelet therapy; LY= life-year; QALY = quality-adjusted life-year

Costs

The largest impact on lifetime costs was incurred through the management of post-stroke patients (57%), followed by post-MI patient management (25%) and acute MI event management (9%). Extended DAPT during the extended DAPT cycle increased costs slightly (+160 CAD), but were slightly lower (–1'654 CAD) in the post-extended DAPT cycle of the model. This resulted in overall savings of 707 CAD compared to the six- to 12-month DAPT (***Table 8***).

Table 8: Model Results – Costs (1.5% Discounted)

	6- to 1-Month DAPT			Extended DAPT			
	Extended DAPT Phase	Post-Extended DAPT Phase	Total	Extended DAPT Phase	Post-Extended DAPT Phase	Total	Difference (Extended DAPT: 6- to 12-month DAPT)
Average total costs	$787	$39,440	$40,227	$947	$38,573	$39,520	–$707
Medication	$61	$502	$563	$430	$509	$939	+$376
MI	$247	$3,276	$3,523	$142	$3,249	$3,391	–$132
Post-MI	$101	$10,476	$10,577	$59	$9,942	$10,001	–$576
Stroke	$93	$1,384	$1,477	$89	$1,371	$1,459	–$18
Post-stroke	$137	$22,583	$22,720	$130	$22,243	$22,373	–$347
Bleeding	$15	$120	$136	$18	$122	$140	+$4
Stent thrombosis	$5	$42	$47	$2	$43	$45	–$3
Urgent revascularization	$128	$1,055	$1,183	$78	$1,070	$1,148	–$36

DAPT = dual antiplatelet therapy; MI = myocardial infarction.

Although medication costs were higher (+376 CAD) in the extended DAPT arm, these were entirely offset by lower costs in acute MI, post-MI, and post-stroke states. Bleeding events had little impact on the overall cost difference.

Table 9: Key Findings of the Economic Evaluation

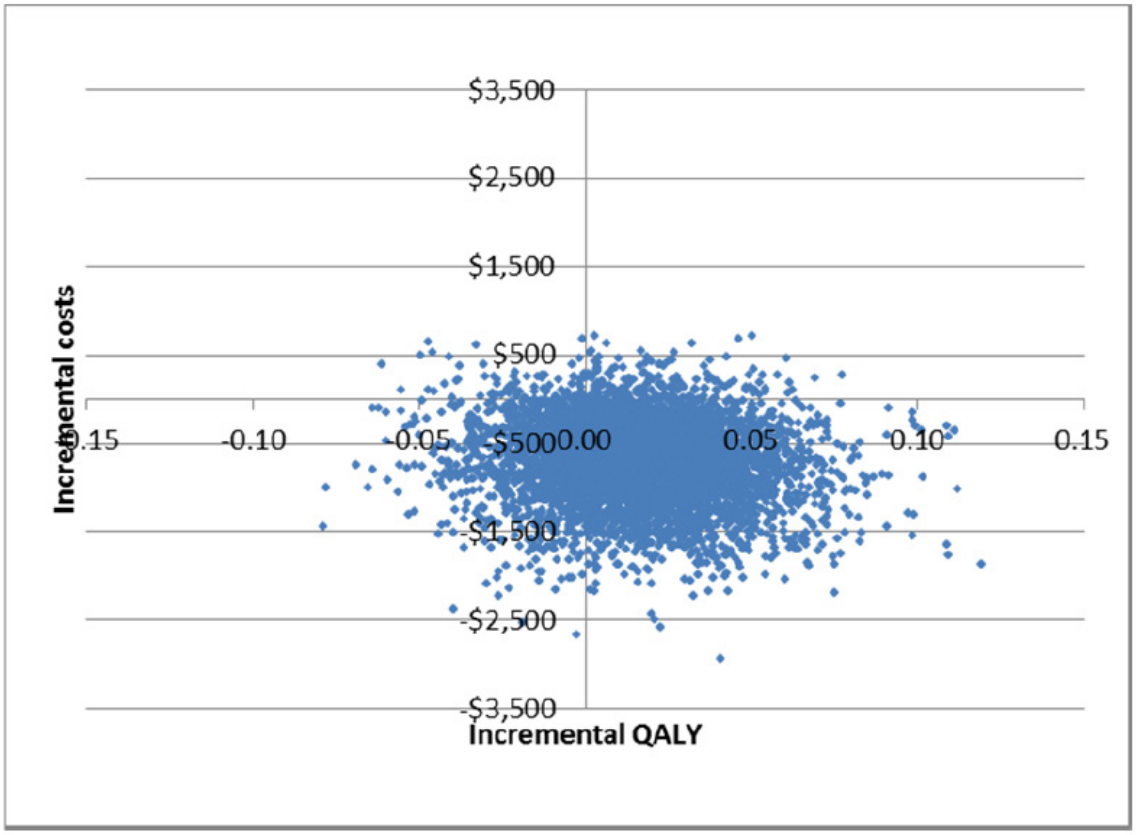
Subgroup	6- to 12-month DAPT		Extended DAPT		Incremental		
	Costs	QALY	Costs	QALY	Δ Costs	Δ QALY	ICUR
All patients (base case)	$40,227	13.64	$39,520	13.65	–$707	0.0160	Extended DAPT dominant
Prior MI	$56,045	12.94	$53,936	13.00	–$2,109	0.0583	Extended DAPT dominant
No prior MI	$46,773	13.48	$45,697	13.42	–$1,076	–0.0575	$18,706
ACS	$48,826	13.17	$47,229	13.24	–$1,597	0.0685	Extended DAPT dominant
Diabetes	$51,880	13.14	$51,749	13.08	–$130	–0.0640	$2,035
No diabetes	$45,525	13.41	$44,239	13.43	–$1,286	0.0177	Extended DAPT dominant
More than 75-years-old	$9,596	6.51	$14,491	6.47	$4,895	–0.0394	6 to 12 months DAPT dominant
Less than 75-years-old	$33,016	14.10	$37,406	14.22	$4,390	0.1158	$37,901

Δ Costs = incremental costs; Δ QALY = incremental QALY; ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; ICUR: incremental cost-utility ratio; QALY= quality-adjusted life-year.

Cost-Effectiveness

This resulted in the extended DAPT strategy being dominant (i.e., more effective and less costly) over the six- to 12-month DAPT strategy (***Table 9***). This dominance was observed in 71.6% of the 5'000 iterations (***Figure 14***). In only 1.5% of the iterations, the extended DAPT strategy was less effective and more costly than six- to 12-months DAPT strategy. Almost 14% of the iterations resulted in an incremental cost-utility ratio (ICUR) above 50'000 CAD per QALY, the Canadian threshold value per QALY. This corresponds with approximately 37'000 CHF per QALY. The incremental benefits associated with extended DAPT came largely (98%) from the lifetime analysis. When the analysis was limited to the duration of the trials included in effectiveness evidence evaluation (i.e., an average of 19 months beyond the initial six- to 12-month DAPT), the incremental benefit of extended DAPT was only 0.0003 QALYs, with incremental costs of 161 CAD, resulting in an ICUR of 546'427 CAD per QALY.

Figure 14:Cost-Effectiveness Plane



Subgroup Analyses

The subgroup analyses indicated that extended DAPT remains dominant in patients with a prior MI and those presenting with ACS. However, extended DAPT resulted in a loss of health benefit in patients with diabetes, those with no prior MI and, those older than 75 years of age.

In most sensitivity analyses, extended DAPT remained dominant. However, when the analysis was performed on a shorter time horizon (i.e., 19 months beyond the initial six to 12 month DAPT), when using efficacy and safety from studies with an extended DAPT duration of 24 to 30 and 36 to 48 months, or when ticagrelor was assumed to be the sole P2Y12 inhibitor used in the DAPT regimen (assuming a similar efficacy across products) the ICUR raised above 25'000 CAD per QALY.

9 Summary

The Swiss Federal Department of Home Affairs commissioned the FOPH to evaluate the available evidence pertaining to the comparative clinical efficacy and safety of six to 12 months DAPT versus 12 months or more, following PCI with stent insertion in CAD patients and various subpopulations. To address this question the FOPH summarised the findings of a recent HTA report published by the CADTH that addressed the same research question. An additional research question in the Canadian report regarded an economic evaluation of the two treatment variants. A short summary of the Canadian economic analyses is also presented. An economic analysis using Swiss prices and costs was not conducted.

The CADTH report showed that in the overall CAD patient population, extending DAPT beyond 12 months was associated with a reduced risk of MI and of probable and definite stent thrombosis. At the same time, extending DAPT beyond 12 months was associated with an increased risk of bleeding. No significant differences were found in the risk of all-cause or cardiovascular death, stroke, urgent target revascularisation, MACCE, or gastrointestinal bleeding between extended DAPT (more than 12 months) and standard-duration DAPT (six to 12 months).

Patients with a previous MI, ACS, no diabetes or those younger than 75 years seemed to benefit the most from extending DAPT beyond 12 months following PCI with stenting. These subgroups all demonstrated a reduced risk of MI. In prior MI patients and those with ACS and no diabetes, stent thrombosis was also reduced when extending DAPT beyond 12 months. This positive result was accompanied with an increased risk of moderate bleeding events.

The economic analyses using a lifetime scenario showed that extending DAPT beyond the initial six to 12 months is dominant with a small incremental benefit of 0.0160 QALY and small savings of 707 CAD. However, 98% of this benefit was accrued in the post-extended DAPT phase of the model. In the first phase of the model, i.e., the extended DAPT phase, the incremental benefit was only 0.0003 QALY with incremental costs of +161 CAD. The ICUR was 546’427 CAD per QALY gained. This would translate into approximately CHF 360’000-380’000 per QALY gained assuming similar medical care provision and costs.

10 Discussion

The CADTH HTA report was conducted according to standardised procedures in a sound and reproducible manner. The clinical findings were extracted from a large body of evidence of primarily high quality. The FOPH analysis of the report detected some limitations of the report that appear relevant when interpreting the results against the Swiss clinical practice.

The primary clinical outcome of CADTH HTA report was death (all-cause, cardiovascular and non-cardiovascular). Although the CADTH report did not show an increased risk of all-cause death with extending DAPT, the findings for non-cardiovascular death were inconsistent. The largest RCT included in the analyses – the DAPT trial, including 11’648 patients - reported an increased risk of non-cardiovascular death with extended DAPT. These findings were not confirmed in two smaller RCTs. Of note, subgroup analyses showed an increased risk of all-cause death among patients without prior MI. However, given the size of the subgroup and the low incidence of events, these findings need to be interpreted with caution.

Considering the secondary outcomes, extended DAPT beyond 12 months reduced the risk of probable or definite stent thrombosis and MI, while increasing the risk of bleeding in the overall patient group. From a clinical perspective, patients with a prior MI, those with ACS at presentation, as well as patient with no diabetes, or aged less than 75 years, appear to derive the most benefit from extended DAPT, provided that the increased risk of bleeding is accounted for when deciding to extend DAPT beyond 12 months.

Four of eight selected trials (DAPT [4], PRODIGY [31], ARCTIC [40] and DES-LATE [33]), representing a substantial part of the overall patient population, applied first-generation stents. Earlier studies have shown that first generation DES are associated with increased rates of late and very late stent thrombosis [17]. Newer generations DES use different materials, geometries and selection and dosage of anti-proliferative agents [17]. These developments slowly reduced the risk of late and very late thrombosis associated with the first generation stents [17]. The CADTH report showed that the benefit of prolonged DAPT, i.e., its protective effect on MI related to late and very late stent thrombosis, is more pronounced in studies using first generation DES. This information is relevant when extrapolating the results to the Swiss clinical practice situation, where clinicians typically apply contemporary newer generation stents.

All studies excluded high-risk bleeding patients. Exclusion of patients with an increased risk of bleeding supresses the risk of bleeding complications associated with extended DAPT. Additional data from clinical or observational studies are needed to assess the risk of bleeding in the clinical practice patient population. Most studies also excluded patients with an increased risk of ischaemic events, which confounds the effect of prolonged DAPT in the opposite direction. This high-risk subgroup of patients deserves further research, as they may profit the most from expanded DAPT.

Overall, limited data were available for subgroup analyses. The largest trial (DAPT trial) [4], characterised by excluding patients with an increased risk of bleeding and ischaemic events, and applying first generation DES in a considerable amount of its patient population, provided most data for the subgroup analyses. Hence, this should be considered when interpreting the results of the subgroup analyses.

The timing of the randomisation of patients varied between RCTs. Some patients were randomised within the first 30 days after PCI with stenting, while other trials randomised patients who completed six to 12 months of DAPT with no adverse events. This may have affected the homogeneity between groups.

Of the four P2Y12 inhibitors used in the studies, clopidogrel was used the most. This implies that the findings of the CADTH report mainly apply to clopidogrel-based regimens, which can be considered a limitation of this analysis. Moreover, given the predominance of enrolled patients who received clopidogrel as the P2Y12 inhibitor, it is not possible to determine whether the choice of P2Y12 inhibitor impacts the effect of extending DAPT beyond 12 months.

The identified limitations of the clinical evidence evaluation also apply to the economic analysis, since the same results were used to inform the economic model. Moreover, since the potential benefits of extended DAPT once treatment is stopped are not known, assumptions were required for the economic evaluation regarding e.g., the risk of events such as death post-MI or stroke, or secondary MI or stroke, in the post-extended DAPT phase of the model. Such assumptions introduce uncertainty which should be acknowledged when interpreting the findings.

The economic analyses confirmed that extending DAPT beyond the initial six to 12 months is more effective and less costly. However, the longest duration of DAPT in the studies was 48 months; as such, the benefits and harms of DAPT beyond that time point are uncertain. The benefit shown in the economic analyses was predominantly accrued in the post-extended DAPT phase of the model. Studies with longer follow-up are needed to confirm the financial impact of extended DAPT beyond two to three years.

The economic analysis was not adapted to the Swiss context, i.e., the economic model was not modified and fed with Swiss data. Modification of the model would e.g. require the inclusion of costs of generic drugs. In the Canadian report costs for clopidogrel reflected costs for the original product only, while in Switzerland both the original and the generic products are prescribed. Differences between the Swiss and Canadian clinical practice situations are to be considered when interpreting the findings of the economic analyses.

11 Insight

The CADTH HTA report showed that extending DAPT beyond 12 months after PCI was found to be associated with a reduced risk of MI and a reduced risk of probable or definite stent thrombosis in CAD patients. This strategy was, however, associated with an increased risk of bleeding.

In the Compulsory Health Insurance Benefits Ordinance – Krankepflege- Leistungsverordnung – DAPT duration is not defined, except for ticagrelor which is limited to 12 months. It was questioned whether this unrestricted coverage is supported by sufficient clinical evidence. According to the presented evidence in this HTA short report, a restriction of treatment duration is not beneficial. The patient population that may benefit from extended DAPT in Switzerland appears to be limited to those patients with high ischaemic risk (e.g. after stent thrombosis, bifurcation stenting or other features associated with increased ischaemic risk) in the absence of a history of bleeding events. This prolongation of DAPT may prevent serious complications such as MI and stent thrombosis, which are beyond doubt undesired events both from a clinical and an economic perspective.

Definitive patient selection criteria for coverage of unrestricted DAPT for CAD patients following DAPT, can be defined when more data from long-term clinical or observational studies have been collected that monitor outcomes in the post-extended DAPT period in pre-specified subgroups.

For clinicians, the decision regarding the optimal DAPT duration for CAD patient following PCI is a trade-off between benefits and harms affected by a patient's characteristics, the type of stent, bleeding history and individual preferences and values.

12 Professional Organisations

Current medical professional society guidelines recommend tailoring the length of DAPT depending on patient characteristics [21 23 43]. The societies also acknowledge the use of the DAPT or PRECISE DAPT score as relevant means to identify high-risk patients [44 45]. The DAPT score is a clinical prediction score based on ischemic and bleeding risk factors to help identify patients with greater expected benefit vs greater expected harm from continuation of DAPT beyond 1 year after PCI, without a major ischemic or bleeding event [44]. The PRECISE-DAPT score is a five-item (age, creatinine clearance, haemoglobin, white-blood-cell count, and previous spontaneous bleeding) risk score, which provides a standardised tool for the prediction of out-of-hospital bleeding during DAPT [45].

The European Society of Cardiology (ESC) updated guidelines on DAPT following PCI in 2019 [22 46]. They recommend six months DAPT in patients with stable coronary artery disease, and at least one-year DAPT for patients with ACS. Extending DAPT beyond 12 months should be considered if potential thrombotic risk is high and bleeding risk is deemed low. The recommendations of the American College of Cardiology/American Heart Association are very similar. Recent Canadian guidelines support a one-year individualised approach to selecting DAPT duration, with different recommendations for patients with ACS or non-ACS indications at the time of PCI [43].
The findings presented in this HTA short report are in line with the recommendations of the professional societies that recommend extended DAPT beyond 12 months only, for selected patients with increased ischaemic risk. The results of this report support adhering to the guidelines.

13 References

1 Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine* 2007;357: 2001–15.

2 Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine* 2009;361: 1045–57.

3 Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *The New England journal of medicine* 2015;372: 1791–800.

4 Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *The New England journal of medicine* 2014;371: 2155–66.

5 Navarese EP, Andreotti F, Schulze V, Kołodziejczak M, Buffon A, Brouwer M, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. *BMJ (Clinical research ed.)* 2015;350: h1618.

6 Valgimigli M, Ariotti S, Costa F. Duration of dual antiplatelet therapy after drug-eluting stent implantation: will we ever reach a consensus? *European heart journal* 2015;36: 1219–22.

7 Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *European heart journal* 2017;38: 804–10.

8 Datenquelle Tarifpool: ©SASIS AG. *2018 - Datenaufbereitung.* 2 ed. Zürich 2019.

9 Canadian Agency for Drugs and Technologies in Health. Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard Versus Extended Duration. Full Report, 2019. https://www.cadth.ca/sites/default/files/ou-tr/op0533-ht0024-dapt-post-pci-created-report.pdf.

10 Bundesamt für Gesundheit. Re-Evaluation von Leistungen der obligatorischen Krankenpflegeversicherung – HTA, 2019. https://www.bag.admin.ch/bag/de/home/versicherungen/krankenversicherung/krankenversicherung-bezeichnung-der-leistungen/re-evaluation-hta.html.

11 Mendis S, Puska P, Norrving B, eds. *Global atlas on cardiovascular disease prevention and control.* Geneva: World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization, 2011.

12 Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* 2015;385: 117–71.

13 Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. *Annals of translational medicine* 2016;4: 256.

14 Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *The New England journal of medicine* 2003;349: 1315–23.

15 Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schömig A, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *The Lancet* 2007;370: 937–48.

16 Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *The New England journal of medicine* 2004;350: 221–31.

17 Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation* 2007;115: 1440-55; discussion 1455.

18 Tomberli B, Mattesini A, Baldereschi GI, Di Mario C. A Brief History of Coronary Artery Stents. *Revista espanola de cardiologia (English ed.)* 2018;71: 312–9.

19 Head SJ, Milojevic M, Daemen J, Ahn J-M, Boersma E, Christiansen EH, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. *The Lancet* 2018;391: 939–48.

20 Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014. *European heart journal* 2015;36: 3320–31.

21 Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *The Journal of thoracic and cardiovascular surgery* 2016;152: 1243–75.

22 Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *European heart journal* 2018;39: 213–60.

23 Costa F, Valgimigli M. Novel directions for the management of dual antiplatelet therapy in patients with coronary artery disease. *Cardiovasc Med* 2019.

24 Michelson AD. Antiplatelet therapies for the treatment of cardiovascular disease. *Nature reviews. Drug discovery* 2010;9: 154–69.

25 Hollopeter G, Jantzen HM, Vincent D, Li G, England L, Ramakrishnan V, et al. Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature* 2001;409: 202–7.

26 Floyd CN, Passacquale G, Ferro A. Comparative pharmacokinetics and pharmacodynamics of platelet adenosine diphosphate receptor antagonists and their clinical implications. *Clinical pharmacokinetics* 2012;51: 429–42.

27 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of clinical epidemiology* 2009;62: 1006–12.

28 Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed.)* 2011;343: d5928.

29 Abbot Vacsular. XIENCE V® USA Dual Antiplatelet Therapy (DAPT) Cohort (XVU-AV DAPT). ClinicalTrials.gov Identifier: NCT01106534, 2010. https://clinicaltrials.gov/ct2/show/NCT01106534 (accessed 28 Jun 2016).

30 Nakamura M, Iijima R, Ako J, Shinke T, Okada H, Ito Y, et al. Dual Antiplatelet Therapy for 6 Versus 18 Months After Biodegradable Polymer Drug-Eluting Stent Implantation. *JACC. Cardiovascular interventions* 2017;10: 1189–98.

31 Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012;125: 2015–26.

32 Lee JM, Cho D-K, Hahn J-Y, Song YB, Park TK, Oh J-H, et al. Safety of 6-month duration of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndromes: Rationale and design of the Smart Angioplasty Research Team-safety of 6-month duration of Dual Antiplatelet Therapy after percutaneous coronary intervention in patients with acute coronary syndromes (SMART-DATE) prospective multicenter randomized trial. *American heart journal* 2016;182: 1–8.

33 Lee CW, Ahn J-M, Park D-W, Kang S-J, Lee S-W, Kim Y-H, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. *Circulation* 2014;129: 304–12.

34 Lee CW. Short-Term Dual Antiplatelet and Maintenance CloPidogrel Therapy After Drug-Eluting Stent Implantation (STAMP-DES). ClinicalTrials.gov Identifier: NCT02494284, 2015. https://clinicaltrials.gov/ct2/show/NCT02494284 (accessed 23 Feb 2017).

35 Beijing Anzhen Hospital. Twelve vs 24 Months of Dual Antiplatelet Therapy in Patients With Coronary Revascularization for In-stent Restenosis. ClinicalTrials.gov Identifier: NCT02402491, 2015. https://clinicaltrials.gov/ct2/show/NCT02402491 (accessed 30 Mar 2015).

36 Helft G, Steg PG, Le Feuvre C, Georges J-L, Carrie D, Dreyfus X, et al. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. *European heart journal* 2016;37: 365–74.

37 Gilard M, Barragan P, Noryani AAL, Noor HA, Majwal T, Hovasse T, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. *Journal of the American College of Cardiology* 2015;65: 777–86.

38 Dadjou Y, Safavi S, Kojuri J. Risks and Benefits of Dual Antiplatelet Therapy Beyond 12 Months After Coronary Stenting: A Prospective Randomized Cohort Study. *Medicine* 2016;95: e3663.

39 Cordis Cooperation. CYPRESS - CYPHER for Evaluating Sustained Safety. ClinicalTrials.gov Identifier: NCT00954707, 2009. https://clinicaltrials.gov/ct2/show/NCT00954707 (accessed 7 Feb 2014).

40 Collet J-P, Silvain J, Barthélémy O, Rangé G, Cayla G, van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. *The Lancet* 2014;384: 1577–85.

41 Gwon H-C, Hahn J-Y, Park KW, Song YB, Chae I-H, Lim D-S, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012;125: 505–13.

42 Jaswal A. *Valuing health in Canada*: *Who, how, and how much?* Ontario, 2013. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=12&cad=rja&uact=8&ved=2ahUKEwjjrMSu1snnAhULfMAKHeiTAPAQFjALegQIAxAB&url=http%3A%2F%2Fcanada2020.ca%2Fwp-content%2Fuploads%2F2013%2F06%2FCanada-2020-Analytical-Commentary-No-3-Valuing-Health-in-Canada-FINAL.pdf&usg=AOvVaw0tb0SRXKTC8U4MlwxunVMY.

43 Mehta SR, Bainey KR, Cantor WJ, Lordkipanidzé M, Marquis-Gravel G, Robinson SD, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy. *The Canadian journal of cardiology* 2018;34: 214–33.

44 Yeh RW, Secemsky EA, Kereiakes DJ, Normand S-LT, Gershlick AH, Cohen DJ, et al. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. *JAMA* 2016;315: 1735–49.

45 Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *The Lancet* 2017;389: 1025–34.

46 Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *European heart journal* 2020;41: 407–77.

14 Appendix I: Characteristics of Included Studies

RCT	Study Design	Population	Stent Types	Treatments	Timing of Randomisation	Primary Outcome	Country	Funding Source
Mauri et al., 2014, (DAPT; NCT00977938)	Multi-centre, Placebo-controlled superiority RCT	≥18 years who had undergone PCI with a DES or BMS. Patients who had no MACCE, repeat revascularisation, or moderate or severe bleeding, and who had been adherent to thienopyridine therapy were randomised 12 mos after PCI	SES, ZES, PES, BMS	ASA 75 mg/d to 162 mg/d+ clopidogrel (75 mg/d) or prasugrel (10 mg/d) for 12 months, followed by continuation on DAPT or discontinuation of P2Y12 inhibitor (ASA continued) for 18 mos DAPT: 12 vs. 30 mos Mean/median treatment duration or follow-up not reported	12 mos post-PCI	Co-primary outcomes: cumulative incidence of definite or probable stent thrombosis and major adverse cardiovascular and cerebrovascular events (composite of death, MI, or stroke)	Multinational	Abbott, Boston Scientific, Cordis, and Medtronic, Bristol-Myers Squibb–Sanofi Pharmaceuticals Partnership, Eli Lilly, Daiichi Sankyo, and the US Department of Health and Human Services

Valgimigli et al., 2012 (PRODIGY; NCT00611286)	Multi-centre, open-label, superiority RCT	≥ 18 yr undergoing elective, urgent, or emergent coronary angioplasty with intended stent implantation, with chronic stable coronary artery disease or acute coronary syndromes, including non-STEMI and STEMI	ZES, EES, PES, BMS	ASA (160 mg to 325 mg orally or 500 mg IV as a loading dose, 80 mg to 160 mg orally indefinitely) + clopidogrel (300 mg or 600 mg orally as a loading dose), then 75 mg/d for 6 or 24 months DAPT: 6 mos vs. 24 mos Mean/median treatment duration or follow-up not reported	30 d +/– 5 days post-PCI	Composite: death of any cause, MI, cerebrovascular accident	Italy	University of Ferrara; no external funding

Collet et al., 2014 (ARCTICInterruption; NCT00827411)	Multi-centre, open-label, superiority RCT	≥ 18 yr who underwent DES implantation, who did not have an ischemic event of the primary end point or any event of the primary safety end point during the first 12 mos	SES, PES, ZES, EES	ASA (75 mg/d to 100 mg/d) alone or ASA (75 mg/d to 100 mg/d) + clopidogrel (75 mg/d to 150 mg/d) or prasugrel (10 mg/d) DAPT: 12 mos vs. 18 mos to 30 Mos Mean/median treatment duration not reported Median follow-up: 17 months (IQR 15 to 18)	12 mo post-PCIs	Composite: death, MI, stent thrombosis, stroke, urgent revascularisation	France	Allies in Cardiovascular Trials Initiatives and Organised Networks (ACTION) Study Group, Fondation de France, Sanofi - Aventis, Cordis, Medtronic, Boston Scientific, Fondation SGAM

Lee et al., 2014 (DES-LATE; NCT01186146)	Multi-centre, open-label RCT	≥18 yr who had undergone implantation with a DES 12 months before enrolment, had not had a major adverse cardiovascular event (myocardial infarction, stroke, or repeat revascularisation) or major bleeding since implantation, and were receiving dual antiplatelet therapy at the time of enrolment	SES, PES, ZES, EES, and "other DES"	ASA (100 mg/d to 200 mg/d) alone or ASA (100 mg/d to 200 mg/d)+ clopidogrel (75 mg/d) DAPT: 12 mo vs. 24 mo Mean/median treatment duration not reported Median follow-up: 42 months (IQR 24.7 to 50.7)	12 mos to18 mos post-PCI	Composite: death resulting from cardiac causes, MI, or stroke	Korea	CardioVascular Research Foundation, Seoul, Korea; and the Health 21 R&D Project, Ministry of Health and Welfare, Korea

Gilard et al., 2015 (ITALIC; NCT01476020)	Multi-centre, open-label non-inferiority RCT	≥18 yr, undergoing PCI with a DES for any indication, with the exception of acute MI and treatment of the left main artery, with confirmed non-resistance to ASA	EES	ASA 75 mg/d to 325 mg/d + clopidogrel 75 mg/d, prasugrel 60 mg/d, or ticagrelor 90 mg twice daily DAPT: 6 mos vs. 24 mos Mean/median treatment duration or follow-up not reported	During PCI hospitalisation; patients were withdrawn if an end point occurred during the first 6 mos of DAPT	Composite: death, MI, urgent target vessel revascularisation, stroke, and major bleeding	Multinational	Abbott Vascular

Helft et al., 2016 (OPTIDUAL; NCT00822536)	Multi-centre, open-label superiority RCT	≥18 yr with symptoms of stable angina, silent ischemia, or acute coronary syndrome (unstable angina, non-STEMI,, or STEMI), who had not experienced a major cardiovascular, cerebrovascular, or major bleeding event in the first 12 mos post-PCI	SES, PES, ZES, EES, BES	ASA (75 mg/d to 160 mg/d) alone or ASA (75 mg/d to 160 mg/d) + clopidogrel (75 mg/d) DAPT: 12 mos vs.18 mos to 48 mos Mean/median treatment duration not reported Median follow-up: 22 mos after randomisation (median follow-up after stenting: 33.4 mos)	12 +/– 3 mos post-PCI	Composite: death, MI, stroke, major bleeding	France	Assistance Publique– Hôpitaux de Paris (Département de la Recherche Clinique et du Développement), Programme Hospitalier de Recherche Publique-PHRC 2008, and unrestricted research grants from Fédération Française de Cardiologie, Cordis, Boston, Medtronic, Terumo, and Biotronik

Nakamura et al., 2017 (NIPPON; NCT01514227)	Multi-centre, non-inferiority open-label RCT	21yr to 79 yr with coronary artery disease, including acute MI	DES[a]	ASA (81 mg/d to 162 mg/d) + clopidogrel (75 mg/d) or ticlopidine (200 mg/d) DAPT: 6 vs. 18 mos Mean/median treatment duration not reported Median follow-up: 435 days (14.5 mos) in the long-term DAPT group and 430 days (14.3 mos) in the short-term DAPT group	During hospitalisation for PCI	Composite: allcause mortality, MI, stroke, major bleeding	Japan	Associations for Establishment of Evidence in Interventions

Dadjou et al., 2016 (NCT02327741)	Multi-centre, open-label, randomised	50 yr to70 yr, with stenosis more than 70% in any coronary vessel with reference diameter of more than 2.25 that was suitable for PCI	Mixed DES, BMS	ASA (325 mg loading dose, 240 mg/d for 2 mo, followed by 75 mg/d) + clopidogrel (600 mg loading dose, then 75 mg/d) DAPT: < 1 yr vs. > 1 yr Mean/median treatment duration not reported Follow-up duration was at least 36 mos	At PCI	Composite: cardiovascular death, the incidence of stent reocclusion, bleeding outcomes (not defined)	Iran	Baghiatollah University and the Education Development Center of Shiraz University of Medical Sciences

Key: BES = biolimus-eluting stent; BMS = bare-metal stent; DAPT = dual antiplatelet therapy; d = day; DAPT = dual anti-platelet therapy; DES = drug-eluting stent; EES = everolimus-eluting stent; IQR = interquartile; IV = intravenous; MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; mos = months; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; RCT = randomised controlled trial; SES = sirolimus-eluting stent; STEMI = ST-elevation myocardial infarction; vs. = versus; yr = year; ZES = zotarolimus-eluting stent.

[a] Biodegradable polymer-coated DES

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Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
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