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CADTH OPTIMAL USE PROJECT

Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard Versus Extended Duration — Project Protocol

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Introduction and Rationale

Current guidelines recommend that patients be given dual antiplatelet therapy (DAPT; combination of a P2Y12 inhibitor [clopidogrel, prasugrel, or ticagrelor] with acetylsalicylic acid [ASA]) ranging from six months to 12 months following percutaneous coronary intervention (PCI) with stenting, with the aim of preventing stent thrombosis and major adverse cardiac and cerebrovascular events (MACCEs).[1–3] However, debate is ongoing about the optimal duration of DAPT; importantly, patient characteristics may be an important factor in treatment duration decisions.[4] In some settings, DAPT for even less than six months may be appropriate (e.g., patients with high risk of bleeding), while other patients may derive greater benefit from extended DAPT (e.g., patients with high risk of stent thrombosis and low risk of bleeding).[3] Previous reviews have reported an increased risk of death among patients who received DAPT for more than 12 months following PCI with stenting,[5,6] but whether this risk is common across all patient subgroups is unclear.

Previous systematic reviews (SRs) have attempted to determine the optimal duration of DAPT;[5–15] however, there is a paucity of data on the impact of specific patient characteristics or type of P2Y12 inhibitor on the effect estimate. One SR[6] reported that extending DAPT beyond 12 months reduced the risk of stent thrombosis in patients without, but not with, acute coronary syndrome (ACS); however, no significant differences were reported in the risk of cardiovascular (CV) death or myocardial infarction (MI). A recent network meta-analysis (NMA) found that among patients randomized to ticagrelor, prasugrel, or clopidogrel, the risk of major adverse cardiac events and MI were lower with both ticagrelor and prasugrel compared with clopidogrel.[16] Shah et al.[16] reported a reduced risk of all-cause and CV death among patients randomized to ticagrelor compared with clopidogrel; however, whether these results are consistent at all durations of DAPT is unknown.

To make appropriate decisions, clinicians require a transparent and comprehensive review of the evidence to evaluate the potential benefits and harms associated with extending DAPT beyond 12 months after stenting to potentially personalize therapy and reach best patient outcomes. Such information may also inform P2Y12 inhibitor reimbursement policies by insurers because such policies may be limited to 12 months, in particular in the public sector. In this study, we will evaluate the comparative clinical effectiveness of different DAPT durations by performing an SR to assess the benefits and harms associated with extending DAPT beyond 12 months following PCI with stenting. We will also investigate the effect of extended DAPT in clinically relevant patient subgroups, including age, history of MI, ACS at presentation, diabetes, and smoking status, and the impact of individual P2Y12 inhibitors. Of note, the patient subgroups were selected based on the clinical components of the DAPT Score[17,18] combined with consideration of findings from a recent clinical review that found different effects between shorter and longer DAPT duration for some subgroups; the selected subgroups were chosen because statistically significant differences were observed in key clinical outcomes when extended DAPT was used.[4] In addition, we will evaluate the comparative cost-effectiveness of different DAPT durations; results from the clinical review will be used to inform clinical input for the economic evaluation.

Scope and Protocol Development

The scope of this Optimal Use project is defined by the population, interventions, comparators and outcomes targeted for evaluation (PICO statement; Table 1). Of note, P2Y12 inhibitors described in Table 1 were selected on the basis of their availability in Canada.

Table 1: PICO Statement

Population	Adult patients who have undergone PCI with any type of stent and who are receiving DAPT.
Interventions	DAPT following PCI with stenting for an extended duration (more than 12 months). DAPT may involve any type of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) in combination with ASA.
Comparators	DAPT for 6 to 12 months. DAPT may involve any type of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) in combination with ASA.
Outcomes[a]	Primary outcome: death (cardiovascular, all-cause, non-cardiovascular). Secondary outcomes: bleeding (major, minor, gastrointestinal), urgent target vessel revascularization, major adverse cardiac and cerebrovascular events, myocardial infarction, stroke, and stent thrombosis.

ASA = acetylsalicylic acid; DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PICO = population, intervention, comparison, outcome.
[a] Studies will not be included or excluded on the basis of reported outcomes.

To inform the final scope of this Optimal Use project, stakeholder feedback and patient-group input will be solicited at different stages of the project. The first period of feedback solicitation will be when the list of included studies is posted on the CADTH website. The protocol will also be posted as a companion document to the list of included studies.

Deliverables

The following deliverables are planned:

- a Science Report (including a clinical evaluation and an economic evaluation) summarizing the clinical and economic findings. These findings will inform the two policy questions as well as deliberations of the CADTH Canadian Drug Expert Committee (CDEC) should Optimal Use recommendations be developed.
- If CADTH decides to pursue recommendations, a CDEC Recommendation Report will be produced based on the Science Report as well as stakeholder feedback and patient-group input. This report will describe the recommendations for the optimal use of DAPT in terms of duration of clinical utilization and reimbursement. Determination of whether such recommendations are developed will be based on whether there is sufficient evidence. Also for consideration will be the identified needs from CADTH jurisdictional customers.

Policy Questions

The first policy question for this project seeks to determine whether it may be cost-effective to extend DAPT duration following PCI with stent insertion. The second policy question seeks to determine whether the choice of P2Y12 inhibitor may impact the cost-effectiveness of extending DAPT.

Policy Question 1: Among patients who underwent PCI with bare-metal stent (BMS) or drug-eluting stent (DES) insertion, what is the cost-effectiveness of using a P2Y12 inhibitor (i.e., clopidogrel, prasugrel, ticagrelor) in combination with ASA beyond 12 months?

Policy Question 2: Among patients who underwent PCI with BMS or DES insertion, what is the comparative cost-effectiveness of individual P2Y12 inhibitors (i.e., clopidogrel, prasugrel, ticagrelor) in combination with ASA beyond 12 months compared with shorter treatment duration (six months to 12 months)?

Research Questions

There are four research questions for this project. The first two aim to inform Policy Question 1. The last two aim to inform Policy Question 2.

RQ1. What are the comparative clinical efficacy and safety of a shorter duration (six months to 12 months) versus a longer duration (longer than 12 months) of DAPT following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS
- those with diabetes
- different age subgroups
- those who smoke.

RQ2. What is the comparative cost-effectiveness of a shorter duration (six months to 12 months) versus a longer duration (longer than 12 months) of DAPT following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS
- those with diabetes
- different age subgroups
- those who smoke.

RQ3. Compared with a shorter treatment duration (six months to 12 months), what are the comparative clinical efficacy and safety of ASA plus clopidogrel, prasugrel, or ticagrelor when used for a longer duration (longer than 12 months) of DAPT following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS
- those with diabetes

- different age subgroups
- those who smoke.

RQ4. Compared with a shorter treatment duration (six months to 12 months), what is the comparative cost-effectiveness of ASA plus clopidogrel, prasugrel, or ticagrelor when used for a longer duration (longer than 12 months) of DAPT following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS
- those with diabetes
- different age subgroups
- those who smoke.

Of note, age subgroups will be limited to patients younger than 75 years or older than 75 years. Also, should data be available, attempts will be made to provide more details for some subgroups, e.g., whether having type 1 diabetes or type 2 diabetes makes a difference in the clinical and cost-effectiveness of extending DAPT.

Clinical Evaluation

The clinical evaluation will address the two following research questions:

RQ1. What are the comparative clinical efficacy and safety of a shorter duration (six months to 12 months) versus a longer duration (more than 12 months) of DAPT following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS
- those with diabetes
- different age subgroups
- those who smoke.

RQ3. Compared with a shorter treatment duration (six months to 12 months), what are the comparative clinical efficacy and safety of ASA plus clopidogrel, prasugrel, or ticagrelor when used for a longer duration (more than 12 months) of DAPT following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS
- those with diabetes
- different age subgroups
- those who smoke.

This clinical review has been registered PROSPERO (No. CRD42018082587) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist.[19] The review will follow the methods of the *Cochrane Handbook for Systematic Reviews of Interventions*[20] and the PRISMA checklist for SRs.[21]

Literature Search Strategy

The literature search will be performed by an information specialist using a peer-reviewed search strategy.

Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946 to the present, including epub ahead of print, in-process records & daily updates) via Ovid; Embase (1974 to the present) via Ovid; The Cochrane Library via Wiley; and PubMed. The search strategy will include both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be dual anti-platelet therapy (DAPT) [Indication] and percutaneous coronary intervention (PCI) or stents [Population].

Methodological filters will be applied to limit retrieval to randomized controlled trials (RCTs). Where possible, retrieval will be limited to the human population. Retrieval will not be limited by publication year or language. Conference abstracts and opinion pieces will be excluded from the search results. See Appendix for details on the proposed search strategies.

Regular alerts will be run until project completion; only citations retrieved before January 2, 2018, will be incorporated into the analysis. Regular search updates will be performed on databases that do not provide alert services. Should relevant new trials be retrieved through the alerts, their results will be examined in the Discussion section of the science report.

Grey literature (literature that is not commercially published) will be identified by searching relevant sections of the *Grey Matters* checklist (www.cadth.ca/grey-matters), i.e., ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) search portal. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Selection and Eligibility Criteria

The inclusion criteria for this review will follow the PICO (population, intervention, comparison, outcome) criteria; however, studies will not be included on the basis of reported outcomes.

Population: Adult patients who have undergone PCI with any type of stent and who are receiving DAPT. Patients receiving DAPT in the absence of stenting are beyond the scope of this review, and studies involving less than 85% of patients who underwent stent implantation will be excluded unless data are reported separately for patients who underwent stenting.

Intervention: DAPT following PCI with stenting for an extended duration (> 12 months). DAPT may involve any type or dose of P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor) in combination with ASA at any dose.

Comparison: DAPT (involving combining a P2Y12 inhibitor [clopidogrel, prasugrel, or ticagrelor] with ASA at any dose) for six months to 12 months. Other DAPT regimens or durations are beyond the scope of this review.

Outcomes: The primary outcome of interest is death (all-cause, CV, non-CV). The secondary outcomes are urgent target vessel revascularization, MACCE, MI, stroke, 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 are expected. Data for MACCE and bleeding will be extracted based on the definitions provided by the study authors. Data will be pooled for MACCE when the components of the composite outcome are deemed sufficiently similar; data for bleeds will be analyzed separately by classification type. Studies will not be included or excluded on the basis of reported outcomes.

Study selection: Two independent reviewers will apply the eligibility criteria based on the PICO statement to each title and abstract identified in the literature search. All records deemed potentially relevant by at least one reviewer will be obtained in full-text format. The eligibility criteria will be applied to the full-text records by both reviewers independently, and a final decision about eligibility will be made. Conflicts will be resolved by discussion. The reviewers will not be blinded to study authors or centre of publication before study selection. Study screening and assessment of eligibility will be facilitated and standardized through the use of DistillerSR (Evidence Partners), an online SR software.

Data Extraction and Critical Appraisal

Data will be extracted by one reviewer via piloted and standardized data abstraction forms, and the extracted data will be checked for accuracy by a second reviewer. Any disagreements will be resolved by consensus. The original, primary publication for each included RCT will be used for data extraction, with supplementary data obtained from companion reports and ClinicalTrials.gov records where necessary to address the research questions and by contacting authors for additional subgroup information. Multiple publications for a unique RCT (e.g., supplemental online appendices, companion publications of specific outcomes or populations from the original study) will be handled by extracting the most recently adjudicated data for each outcome specified a priori in this protocol.

Data to be extracted include study characteristics (e.g., author, year, study design, country of study) and participant characteristics (e.g., age, sex, smoking status, diabetes, prior MI, presence of ACS at presentation, history of heart failure). Intervention and comparator details (e.g., DAPT duration, type of P2Y12 inhibitor) as well as event counts at the longest duration of treatment for each group will also be extracted.

Effect estimates will be extracted separately for clinically important subgroups (i.e., age, smoking status, diabetes, prior MI, presence or absence of ACS at the time of presentation). If available, data will also be extracted separately for type of P2Y12 inhibitor (i.e., clopidogrel, prasugrel, ticagrelor).

Two independent reviewers will apply the Cochrane Collaboration's risk of bias tool (RoB 2.0)[22] to each included RCT, and any disagreements will be resolved by discussion. Publication bias will be assessed by visual inspection of funnel plots for outcomes that have data from at least 10 studies.[20]

Data Synthesis and Analysis

A descriptive summary of study selection, quality assessment, and study and patient characteristics will be presented.

Data for all patients, as well as for a priori–defined patient subgroups, will be analyzed by random-effects pairwise meta-analysis using RevMan (version 5.3; Cochrane Collaboration). The relative risk and 95% confidence intervals for each outcome will be determined (i.e., more than 12 months of DAPT versus six months to 12 months of DAPT). The number of participants who experienced an event after randomization and the number of participants randomized to each group will be used for all analyses. Outcome data will be extracted and analyzed separately for clinically important subgroups (i.e., age, smoking status, diabetes, prior MI, presence or absence of ACS at the time of presentation). The age groups will be based on the data reported in the included studies. Smoking status may include current, former or never, and the groups for analysis will be based on the reported data.

Clinical heterogeneity will be assessed by examining the patient characteristics of the included studies, and methodological heterogeneity by the study design characteristics. Statistical heterogeneity will be assessed using the I^2 statistic, with I^2 values above 75% considered to represent substantial heterogeneity. Pooled data will not be reported above this threshold. If data are insufficient or if high heterogeneity is detected, descriptive summaries will be presented.

The feasibility of NMA to address Research Question 3 will be assessed in consultation with a statistician and the research team. This assessment will consider whether there is a sufficient quantity of data and whether the data are sufficiently similar to pool via NMA. If there are insufficient data for NMA to address Research Question 3, the data will be analyzed by random-effects meta-analysis as described previously (i.e., for each P2Y12 inhibitor, six months to 12 months of DAPT will be compared with more than 12 months of DAPT).

If sufficient data are available, Bayesian NMA will be undertaken to analyze the effect of individual P2Y12 inhibitors at different durations of DAPT. Heterogeneity will be assessed using the I^2 statistic as described previously. Assessment of model fit and choice of model (fixed effects versus random effects) will be based on the deviance information criterion and comparison of residual deviance to the number of unconstrained data points.[23] If necessary, a continuity correction will be applied to adjust for zero events. Where possible, inconsistency will be assessed by comparing the deviance, between-study variance, and deviance information criterion statistics of the consistency and inconsistency models.[24]

Point estimates and 95% credible intervals will be calculated using the Markov chain Monte Carlo method. Vague priors (e.g., N[0, 100^2]) will be assigned for basic parameters,[23] and trace plots and Brooks–Gelman–Rubin statistics will be assessed for model convergence.[25] Three chains will be fit with at least 20,000 iterations and a burn-in of at least 20,000 iterations.

Network evidence diagrams will be produced using NodeXL, and NMAs will be performed using WinBUGS (version 1.4.3; MRC Biostatistics Unit).

Economic Evaluation

As stated in section 5, the economic evaluation will address the following two research questions:

RQ2. What is the comparative cost-effectiveness of a shorter duration (six months to 12 months) versus a longer duration (more than 12 months) of DAPT following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS
- those with diabetes
- different age groups
- those who smoke.

RQ4. Compared with a shorter treatment duration (six months to 12 months), what is the comparative cost-effectiveness of ASA plus clopidogrel, prasugrel, or ticagrelor when used for a longer duration (more than 12 months) of DAPT following PCI with BMS or DES insertion in:

- all post-PCI patients
- those with a prior MI
- those presenting with ACS
- those with diabetes
- different age groups
- those who smoke.

Primary Economic Analysis

To address these research questions, a cost-utility analysis will compare costs and health outcomes associated with the administration of DAPT for six months to 12 months to those of DAPT administered for more than 12 months post-PCI.

The primary economic analysis will focus on Policy Question 1, Research Question 2 - all post-PCI patients (i.e., all patients and all P2Y12 inhibitors combined). All other elements of the two research questions will be addressed as subgroup analyses.

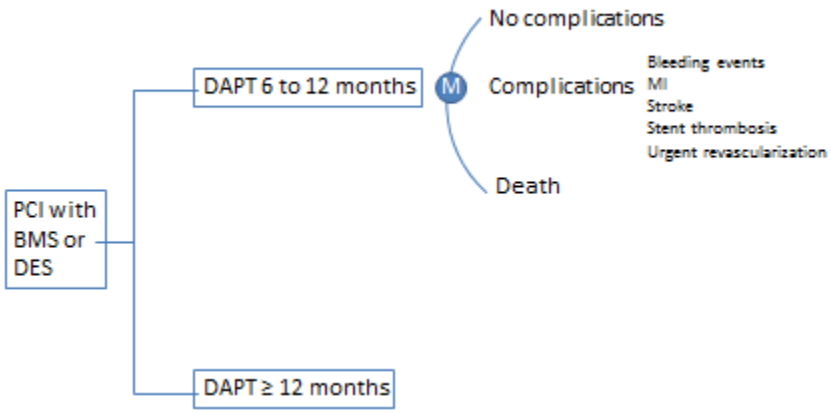
All analyses will be conducted in accordance with CADTH guidelines for the economic evaluation of health technologies.[26]

Model Design

CADTH will adapt a published patient-level Markov model recently developed and validated for the Canadian setting, which will form the basis of the economic model for the current evaluation.[27] This model will be modified as necessary to answer the policy and research questions.

The final model is expected to include the following health states: no complication, complications (major and minor bleeding events, MI, stroke, stent thrombosis, urgent revascularization), and death (from CV and non-CV causes). See Figure 1.

Figure 1: Expected Structure of the Economic Model



BMS = bare-metal stent; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Clinical experts will be consulted to ensure that the model structure reflects existing Canadian clinical practice.

Perspective

The perspective will be that of the Canadian health care payer.

Time Horizon and Discounting

A lifetime time horizon will be taken to capture long-term consequences. Costs and quality-adjusted life-years (QALYs) will be discounted at 1.5% per annum.

Clinical Inputs

Probabilities and relative risk of each complication as well as death in patients treated with six months to 12 months of DAPT and those treated with more than 12 months of DAPT will be obtained from the clinical evaluation. In order to reflect the lifetime time horizon, natural history information will also be used, based on existing literature (from a Canadian population where possible).

Resource Use and Cost Data

Health care resources and costs captured in the model will reflect the clinical events assessed in the clinical evaluation and the perspective of the economic analysis. Costs of interest will be those necessary for the management of stent complications that are expected to be prevented or reduced by DAPT (i.e., MI, stroke, stent thrombosis, urgent revascularization), those from DAPT (i.e., bleeding events), and those related to the DAPT regimens.

Canadian-specific costs from official sources such as Canadian health care system databases will be used as much as possible. Costs that could not be identified from Canadian official sources will be estimated from the medical literature, and, ideally, from

comparable health systems. If necessary, costs will be adjusted to 2018 Canadian dollars using the consumer price index.

Utilities

Utilities associated with each health state and disutility of complications will be obtained from targeted literature searches. Canadian sources will be preferred.

Analysis Outputs

The model will estimate the expected clinical events, costs, and QALYs associated with the treatment strategies over a lifetime time horizon. QALYs will be the main clinical outcome of the model capturing the impact of treatments on patients' morbidity and mortality. The primary economic outcome will be the incremental cost-utility ratio (ICUR). The ICUR will be calculated as follows:

$$\frac{Costs(> 12\ month\ DAPT) - Costs(6\ to\ 12\ month\ DAPT)}{QALYs(>\ 12\ month\ DAPT) - QALYs(6\ to\ 12\ month\ DAPT)}$$

Sensitivity Analysis

All analyses will be conducted probabilistically (5,000 iterations) to account for parameter uncertainty. Scenario analyses will be performed to account for structural uncertainty (e.g., discount rates 0% and 5%).

Subgroup analyses will be done in accordance with the clinical evaluation in terms of patient characteristics:

- prior MI versus no prior MI
- ACS versus no ACS
- diabetes versus no diabetes
- age groups
- smoking status
- type of intervention (i.e., P2Y12 agents clopidogrel, prasugrel, and ticagrelor).

Assumptions

Assumptions and limitations identified during model development will be listed and discussed in the report. When possible, their potential impact on the results will be tested in sensitivity analyses.

Model Validation

The face validity of the model structure, assumptions, and outputs will be performed through consultation with clinical experts in the field to ensure that the model is consistent with Canadian practice, that the best available data sources are used, that no significant evidence is omitted, and that results are consistent with what is known of the field. Internal validity will be ensured by an external technical review of the model. The model structure and results will be compared with other similar models for cross-validity.

References

1. Tanguay JF, Bell AD, Ackman ML, Bauer RD, Cartier R, Chan WS, et al. Focused 2012 update of the Canadian Cardiovascular Society guidelines for the use of antiplatelet therapy. *Can J Cardiol*. 2013;29(11):1334-1345
2. 2014 ESC/EACTS guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35(37):2541-2619.
3. Levine GN, Bates ER, Mauri L, Bittl JA, Mehran R, Brindis RG, 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. *Circulation*. 2016;133:000-000.
4. Wells GA, Elliott J, Kelly S, So D, Boucher M, Bai Z, et al. Dual antiplatelet therapy following percutaneous coronary intervention: A review of the clinical impact of treatment duration. Ottawa, ON: CADTH; 2017 Aug. (CADTH technology overview, no 8). Available from: https://cadth.ca/dual-antiplatelet-therapy-following-percutaneous-coronary-intervention-review-clinical-impact . Assessed 2018 Feb 6.
5. Fei Y, Tsoi MF, Cheung TT, Cheung BM. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of randomized controlled trials. *Int J Cardiol*. 2016;220:895-900.
6. 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*. 2015;350:h1618
7. Zhang XL, Zhu QQ, Zhu L, Shi SQ, Chen JZ, Huang W, et al. Optimize the duration of DAPT following des implantation: An updated system review and meta-analysis of 10 randomized trials. *Clin Trials Regul Sci Cardiol.* 2015;6:1-11
8. Xie C, Ding XL, Miao LY. Different durations of dual anti-platelet therapy after percutaneous coronary intervention with drug-eluting stents in patients with coronary disease: A systematic review. *Chinese Pharm J*. 2016;51:762-768.
9. Verdoia M, Schaffer A, Barbieri L, Montalescot G, Collet JP, Colombo A, et al. Optimal duration of dual antiplatelet therapy after DES implantation: a meta-analysis of 11 randomized trials. *Angiology*. 2015;67:224-238.
10. Tsoi MF, Cheung CL, Cheung TT, Wong IC, Kumana CR, Tse HF, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of large randomised controlled trials. *SciRep*. 2015;5:13204.
11. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: A pairwise and Bayesian network meta-analysis of randomised trials. *Lancet*. 2015;385:2371-2382.
12. Palla M, Briasoulis A, Siddiqui F, Alesh I, Afonso L. Long (>12 months) and short (<6 months) versus standard duration of dual antiplatelet therapy after coronary stenting: A systematic review and meta-analysis. *Am J Ther*. 2015;2015 Aug 1.
13. Cassese S, Byrne RA, Ndrepepa G, Schunkert H, Fusaro M, Kastrati A. Prolonged dual antiplatelet therapy after drug-eluting stenting: Meta-analysis of randomized trials. *Clin Res Cardiol*. 2015;104:887-901.
14. Bittl J, Baber U, Bradley S, Wijeysundera D. Duration of dual antiplatelet therapy: A systematic review for the 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 Associon Task Force on Clinical Practice Guidelines. *Circulation.* 2016;68(10):111639.
15. D'Ascenzo F, Moretti C, Bianco M, Bernardi A, Taha S, Cerrato E, et al. Meta-analysis of the duration of dual antiplatelet therapy in patients treated with second-generation drug-eluting stents. *Am J Cardiol*. 2016;117(11):1714-1723.
16. Shah R, Rashid A, Hwang I, Fan T-HM, Khouzam RN, Reed GL. Meta-analysis of the relative efficacy and safety of oral P2Y12 inhibitors in patients with acute coronary syndrome. *Am J Cardiol*. 2017;119(11):1723-1728.
17. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, 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(16):1735-1749.
18. DAPT Score. QxMD; 2018. Available from: https://qxmd.com/calculate/calculator_373/dapt-score. Accessed 2018 Feb 6.
19. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1.
20. Higgins JP, Green S, eds. Assessing risk of bias in included studies. In: Cochrane handbook for systematic reviews of interventions. Chichester, UK: Wiley-Blackwell; 2008:187-242.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, The Prisma Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (Reprinted from Annals of Internal Medicine). *PLOS Med*. 2009;6(7):e1000097.
22. Higgins JPT, Sterne JAC, Savoic J, Reeves B, Turner J, et al. A revised tool for assessing risk of bias in randomized trials. *Cochrane Database Syst Rev*. 2016;Suppl 1(10):1-21.
23. Dias S, Sutton A, Welton N, Ades A, Golfinopoulos V, Kyrgiou M. A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. London (GB): National Institute for Health and Care Excellence (NICE); 2014. (NICE DSU Technical support document 2). Available from: https://www.ncbi.nlm.nih.gov/books/NBK310366/. Accessed 2018 Feb 6.

24. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: Inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Mak*. 2013;33(5):641-656.

25. Spiegelhalter D, Thomas A, Best N, Lunn D. WinBUGS user Manual. Ver 1.4. Cambridge (GB): University of Cambridge; 2003. Available from: http://www.mrc-bsu.cam.ac.uk/wp-content/uploads/manual14.pdf. Accessed 2018 Feb 12

26. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): CADTH; 2017. Available from: https://www.cadth.ca/about-cadth/how-we-do-it/methods-and-guidelines/guidelines-for-the-economic-evaluation-of-health-technologies-canada. Accessed 2018 Feb 12.

27. Arbel Y, Bennell MC, Goodman SG, Wijeysundera HC. Cost-effectiveness of different durations of dual-antiplatelet use after percutaneous coronary intervention. *Can J Cardiol*. 2018;34(1):31-37.

Appendix: Literature Search Strategy

DAPT2 – RCTs
Final Strategies
2017 Nov 17

Ovid Multifile

Database: Embase <1974 to 2017 November 16>, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1 exp Stents/ (217801)
2 (stent or stents or stented or stenting).tw,kf. (229006)
3 (DES or DESs).tw,kf. (66037)
4 (Strecker* or Supremo* or WallFlex* or Wallstent*).tw,kf. (4129)
5 or/1-4 [STENTS, INCL DRUG-ELUTING STENTS] (328250)
6 ((dual or double) adj (antiplatelet* or anti-platelet*)).tw,kf. (11656)
7 (DAPT or DAPTs).tw,kf. (4450)
8 6 or 7 [DAPT] (13704)
9 Platelet Aggregation Inhibitors/ (69297)
10 (antiplatelet* or anti-platelet*).tw,kf. (70655)
11 (platelet* adj2 inhibit*).tw,kf. (37259)
12 thrombocyte aggregation inhibit*.tw,kf. (298)
13 Purinergic P2Y Receptor Antagonists/ (2101)
14 ((P2Y or P2Y1 or P2Y12 or P2Y2) adj (receptor antagonist* or purinoceptor antagonist*)).tw,kf. (1551)
15 (ADP receptor adj (antagonist* or blocker*)).tw,kf. (699)
16 (adenosine diphosphate receptor adj (antagonist* or blocker*)).tw,kf. (165)
17 clopidogrel*.tw,kf. (31373)
18 (clopilet or grepid or iscover or PCR 4099 or PCR4099 or plavix or SC 25989C or SC 25990C or SR 25989 or zopya or zylagren or zyllt).tw,kf. (3432)
19 (duocover or duoplavin).tw,kf. (11)
20 clopidogrel.rn. (52849)
21 Prasugrel Hydrochloride/ (7818)
22 (prasugrel or CS 747 or CS747 or effient or efient or LY 640315 or LY640315).tw,kf. (5368)
23 prasugrel.rn. (6725)
24 ticagrelor.tw,kf. (4826)
25 (AZD 6140 or AZD6140 or brilinta or brilique or possia).tw,kf. (731)
26 ticagrelor.rn. (5832)
27 Aspirin/ (230098)
28 asa.tw,kf. (64487)
29 aspirin.tw,kf. (154739)
30 ("2-(Acetyloxy)benzoic Acid" or acetylsalicylic acid or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).tw,kf. (21715)
31 ("2 acetoxybenzoate" or "8-hour bayer" or acenterine or acesal or acetan or acetard or aceticil or aceticyl or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylic salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetylsalicyclic acid or acetylsalicyl or acetylsalicylate or acetylsalicylic acid or acetylsalycic acid or acetylsalycylic acid or acetysal or acidulatum or acidum acetyl salicylicum or acidum acetylosalicylicum or acidum acetylsalicylicum).tw,kf. (25222)

32 (actorin or acylpyrine or acytosal or adiro or alabukun or alasil or albyl-e or alka seltzer or alkaspirin or anasprin or andol or anopyrin or ansin or anthrom or aptor or arthralgyl or asaflow or asaphen or asapor or asatard or asawin or aspec or aspent or aspex or aspilets or aspirem or aspirgran or aspirina or aspirine or aspirinine or aspirisucre or aspisol or aspo cid or aspro or asrina or asrivo or asta or asteric or astrix).tw,kf. (3738)
33 (bebesan or biprin or bokey or boxazin or breoprin or bufferin or cafenol or caprin or cardioaspirina or caspirin or catalgine or catalgix or cemerit or cemirit or claradin or claragine or comoprin or contrheuma).tw,kf. (523)
34 (darosal or dispirin or dolean or dolean or dusil or ecasil or ecosprin or egalgic or emocin or empirin or encaprin or encine or endosprin or entaprin or entericin or enteroprin or enterosarine or enterospirine or entrophen or eskotrin or euthermine or extren).tw,kf. (245)
35 (genasprin or globentyl or godamed or gotosan or helicon or idotyl or infatabs or istopirin or istopyrine or ivepirine or juvepirine or keypo or kilios or "mcn r 358" or measurin or mejoral or melabon or micropyrin or mikristin or miniasal or mycristin).tw,kf. (311)
36 (naspro or novasen or nu seal or nu seals or nuseal? or ortho acetoxybenzoate or ortho acetoxybenzoic or ostoprin or pancemol or paracin or paynocil or pengo or platet 300 cleartab or plewin or polopiryna or premaspin or primaspan or proprin or pyronoval).tw,kf. (166)
37 (reumyl or rhodine or rhonal or ronal or salacetin or salacetogen or saletin or salisalido or sargepirine or soldral or solpyron or solucetyl or solupsa or spren).tw,kf. (180)
38 (tapal or temagin or tevapirin or "th 2152" or thrombo-aspilets or treupahlin or treuphalin or tromalyt or tromcor or turivital or verin or vitalink or xaxa or zero-order release).tw,kf. (1892)
39 aspirin.rn. (45107)
40 or/9-39 [ANTI-PLATELETS] (427798)
41 Drug Combinations/ (144300)
42 Drug Therapy, Combination/ (170884)
43 Combined Modality Therapy/ (230353)
44 ((combination* or combine* or combining) adj2 (agent or agents or drug or drugs)).tw,kf. (71680)
45 ((combination* or combine* or combining) adj2 (therap* or treatment*)).tw,kf. (300428)
46 ((dual or double) adj2 (therap* or treatment*)).tw,kf. (29075)
47 or/41-46 [DUAL THERAPY] (843321)
48 40 and 47 [DUAL ANTI-PLATELETS] (27099)
49 8 or 48 [ALL DAPT/DUAL ANTI-PLATELETS] (30524)
50 5 and 49 [DAPT/DUAL ANTI-PLATELET THERAPY - STENTS] (8875)
51 exp Percutaneous Coronary Intervention/ (134063)
52 (percutaneous coronary adj3 (intervention? or revascular* or re-vascular*)).tw,kf. (75519)
53 (PCI or PCIs or PPCI or PPCIs).tw,kf. (70690)
54 (coronary adj2 balloon adj (dilation* or dilatation*)).tw,kf. (73)
55 (coronary angioplast* adj2 balloon).tw,kf. (545)
56 PTCA.tw,kf. (15013)
57 Angioplasty, Balloon, Laser-Assisted/ (405)
58 (laser-assisted adj2 angioplast*).tw,kf. (393)
59 (laser balloon* adj2 angioplast*).tw,kf. (84)
60 percutaneous transluminal laser angioplast*.tw,kf. (57)
61 PTLA.tw,kf. (108)
62 or/51-61 [PCI] (174963)
63 49 and 62 [DAPT/DUAL ANTI-PLATELET THERAPY - PCI] (7597)
64 50 or 63 [DAPT/DUAL ANTI-PLATELET THERAPY - PCI, STENTS] (11554)
65 (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (600783)
66 clinical trials as topic.sh. (197045)
67 exp Randomized Controlled Trials as Topic/ (266172)
68 (randomi#ed or randomly or RCT$1 or placebo*).tw,kf. (2029435)
69 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf. (378577)

70 trial.ti. (439852)
71 or/65-70 (2636139)
72 64 and 71 [RCTS] (3404)
73 Adolescent/ not (exp Adult/ and Adolescent/) (1122505)
74 exp Child/ not (exp Adult/ and exp Child/) (3020143)
75 exp Infant/ not (exp Adult/ and exp Infant/) (1614976)
76 or/73-75 (3895634)
77 72 not 76 [CHILD-ONLY REMOVED] (3401)
78 exp Animals/ not (exp Animals/ and Humans/) (15391813)
79 77 not 78 [ANIMAL ONLY REMOVED] (2407)
80 (comment or editorial or interview or news or newspaper article).pt. (1839418)
81 (letter not (letter and randomized controlled trial)).pt. (2029588)
82 79 not (80 or 81) [OPINION PIECES REMOVED] (2349)
83 82 use ppez [MEDLINE RECORDS] (1629)
84 exp stent/ (217801)
85 (stent or stents or stented or stenting).tw,kw. (231797)
86 (DES or DESs).tw,kw. (65389)
87 (Strecker* or Supremo* or WallFlex* or Wallstent*).tw,kw. (4193)
88 or/84-87 [STENTS, INCLUDING DRUG-ELUTING STENTS] (328947)
89 ((dual or double) adj (antiplatelet* or anti-platelet*)).tw,kw. (11693)
90 (DAPT or DAPTs).tw,kw. (4485)
91 acetylsalicylic acid plus clopidogrel/ (508)
92 (duocover or duoplavin).tw,kw. (11)
93 or/89-92 [DUAL ANTI-PLATELETS/DAPT] (14187)
94 antithrombocytic agent/ (37024)
95 (antiplatelet* or anti-platelet*).tw,kw. (72063)
96 (platelet* adj2 inhibit*).tw,kw. (37843)
97 thrombocyte aggregation inhibit*.tw,kw. (302)
98 purinergic P2Y receptor antagonist/ (2175)
99 ((P2Y or P2Y1 or P2Y12 or P2Y2) adj (receptor antagonist* or purinoceptor antagonist*)).tw,kw. (1576)
100 (ADP receptor adj (antagonist* or blocker*)).tw,kw. (725)
101 (adenosine diphosphate receptor adj (antagonist* or blocker*)).tw,kw. (167)
102 clopidogrel/ (51572)
103 (clopidogrel or clopilet or grepid or iscover or PCR 4099 or PCR4099 or plavix or SC 25989C or SC 25990C or SR 25989 or zopya or zylagren or zyllt).tw,kw. (34060)
104 clopidogrel.rn. (52849)
105 prasugrel/ (7818)
106 (prasugrel or CS 747 or CS747 or effient or efient or LY 640315 or LY640315).tw,kw. (5506)
107 prasugrel.rn. (6725)
108 ticagrelor/ (5731)
109 ticagrelor.tw,kw. (4953)
110 (AZD 6140 or AZD6140 or brilinta or brilique or possia).tw,kw. (735)
111 ticagrelor.rn. (5832)
112 acetylsalicylic acid/ (237995)
113 asa.tw,kw. (64612)
114 aspirin.tw,kw. (155623)
115 ("2-(Acetyloxy)benzoic Acid" or acetylsalicylic acid or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin).tw,kw. (21653)
116 ("2 acetoxybenzoate" or "8-hour bayer" or acenterine or acesal or acetan or acetard or aceticil or aceticyl or acetonyl or acetophen or acetosal or acetosalicylic acid or acetosalin or acetosalum or acetyl salicylate or acetyl salicylic acid or acetylic

salicylic acid or acetylin or acetylo or acetylon or acetylosalicylic acid or acetylsal or acetylsalicyclic acid or acetylsalicyl or acetylsalicylate or acetylsalicylic acid or acetylsalycic acid or acetylsalycylic acid or acetysal or acidulatum or acidum acetyl salicylicum or acidum acetylosalicylicum or acidum acetylsalicylicum).tw,kw. (25195)
117 (actorin or acylpyrine or acytosal or adiro or alabukun or alasil or albyl-e or alka seltzer or alkaspirin or anasprin or andol or anopyrin or ansin or anthrom or aptor or arthralgyl or asaflow or asaphen or asapor or asatard or asawin or aspec or aspent or aspex or aspilets or aspirem or aspirgran or aspirina or aspirine or aspirinine or aspirisucre or aspisol or aspo cid or aspro or asrina or asrivo or asta or asteric or astrix).tw,kw. (3747)
118 (bebesan or biprin or bokey or boxazin or breoprin or bufferin or cafenol or caprin or cardioaspirina or caspirin or catalgine or catalgix or cemerit or cemirit or claradin or claragine or comoprin or contrheuma).tw,kw. (523)
119 (darosal or dispirin or dolean or dolean or dusil or ecasil or ecosprin or egalgic or emocin or empirin or encaprin or encine or endosprin or entaprin or entericin or enteroprin or enterosarine or enterospirine or entrophen or eskotrin or euthermine or extren).tw,kw. (245)
120 (genasprin or globentyl or godamed or gotosan or helicon or idotyl or infatabs or istopirin or istopyrine or ivepirine or juvepirine or keypo or kilios or "mcn r 358" or measurin or mejoral or melabon or micropyrin or mikristin or miniasal or mycristin).tw,kw. (310)
121 (naspro or novasen or nu seal or nu seals or nuseal? or ortho acetoxybenzoate or ortho acetoxybenzoic or ostoprin or pancemol or paracin or paynocil or pengo or platet 300 cleartab or plewin or polopiryna or premaspin or primaspan or proprin or pyronoval).tw,kw. (166)
122 (reumyl or rhodine or rhonal or ronal or salacetin or salacetogen or saletin or salisalido or sargepirine or soldral or solpyron or solucetyl or solupsa or spren).tw,kw. (181)
123 (tapal or temagin or tevapirin or "th 2152" or thrombo-aspilets or treupahlin or treuphalin or tromalyt or tromcor or turivital or verin or vitalink or xaxa or zero-order release).tw,kw. (1945)
124 acetylsalicylic acid.rn. (179033)
125 or/94-124 [ANTI-PLATELETS] (421538)
126 acetylsalicylic acid/cb [Drug Combination] (22792)
127 antithrombocytic agent/cb [Drug Combination] (2530)
128 clopidogrel/cb [Drug Combination] (10240)
129 prasugrel/cb [Drug Combination] (689)
130 purinergic P2Y receptor antagonist/cb [Drug Combination] (42)
131 ticagrelor/cb [Drug Combination] (633)
132 drug combination/ (75772)
133 ((combination* or combine* or combining) adj2 (agent or agents or drug or drugs)).tw,kw. (72667)
134 ((combination* or combine* or combining) adj2 (therap* or treatment*)).tw,kw. (304069)
135 ((dual or double) adj2 (therap* or treatment*)).tw,kw. (29149)
136 or/126-135 [DUAL/COMBINATION THERAPY] (469424)
137 125 and 136 [DUAL ANTI-PLATELETS] (41507)
138 93 or 137 [ALL DAPT/DUAL ANTI-PLATELETS] (45235)
139 88 and 138 [DAPT/DUAL ANTI-PLATELET THERAPY - STENTS] (11990)
140 exp percutaneous coronary intervention/ (134063)
141 (percutaneous coronary adj3 (intervention? or revascular* or re-vascular*)).tw,kw. (77074)
142 (PCI or PCIs or PPCI or PPCIs).tw,kw. (71355)
143 (coronary adj2 balloon adj (dilation* or dilatation*)).tw,kw. (74)
144 (coronary angioplast* adj2 balloon).tw,kw. (550)
145 PTCA.tw,kw. (15335)
146 laser angioplasty/ (1613)
147 (laser-assisted adj2 angioplast*).tw,kw. (403)
148 (laser balloon* adj2 angioplast*).tw,kw. (85)
149 percutaneous transluminal laser angioplast*.tw,kw. (58)
150 PTLA.tw,kw. (108)
151 or/140-150 [PCI] (176576)

152 138 and 151 [DAPT/DUAL ANTI-PLATELET THERAPY - PCI] (10046)
153 139 or 152 [DAPT/DUAL ANTI-PLATELET THERAPY - PCI, STENTS] (15793)
154 randomized controlled trial/ or controlled clinical trial/ (1256927)
155 exp "clinical trial (topic)"/ (259591)
156 (randomi#ed or randomly or RCT$1 or placebo*).tw,kw. (2031382)
157 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. (378723)
158 trial.ti. (439852)
159 or/154-158 (2783022)
160 153 and 159 [RCTs] (4406)
161 exp juvenile/ not (exp juvenile/ and exp adult/) (2086919)
162 adolescent/ not (exp adult/ and adolescent/) (1122505)
163 exp child/ not (exp adult/ and exp child/) (3020143)
164 exp infant/ not (exp adult/ and exp Infant/) (1614976)
165 or/161-164 (3938434)
166 160 not 165 [CHILD-ONLY REMOVED] (4401)
167 exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (47276827)
168 exp human/ or exp human experimentation/ or exp human experiment/ (37268462)
169 167 not 168 (10010053)
170 166 not 169 [ANIMAL-ONLY REMOVED] (4382)
171 editorial.pt. (1023263)
172 letter.pt. not (letter.pt. and randomized controlled trial/) (2024811)
173 170 not (171 or 172) [OPINION PIECES REMOVED] (4288)
174 conference abstract.pt. (2773711)
175 173 not 174 [CONFERENCE ABSTRACTS REMOVED] (3635)
176 175 use oemezd [EMBASE RECORDS] (2793)
177 83 or 176 [BOTH DATABASES] (4422)
178 remove duplicates from 177 (3261)
179 178 use ppez [MEDLINE UNIQUE RECORDS] (1448)
180 178 use oemezd [EMBASE UNIQUE RECORDS] (1813)