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

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Abbreviations

ACC  American College of Cardiology
ACS  Acute coronary syndrome
AHA  American Heart Association
ASA  acetylsalicylic acid
BARC  Bleeding Academic Research Consortium
BMS  bare-metal stent
CDEC  CADTH Canadian Drug Expert Committee
CI  confidence interval
DAPT  dual antiplatelet therapy
DES  drug-eluting stent
ESC  European Society of Cardiology
FDA  Food and Drug Administration
GUSTO  Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries
ICUR  incremental cost-utility ratio
HR  hazard ratio
MACCE  major adverse cardiac and cerebrovascular event
MI  myocardial infarction
NNH  number needed to harm
NNT  number needed to treat
PCI  percutaneous coronary intervention
QALY  quality-adjusted life-year
RCT  randomized controlled trial
RR  relative risk
STEMI  ST-elevation myocardial infarction
TIMI  thrombolysis in myocardial infarction
Background

Dual antiplatelet therapy (DAPT; combination of a P2Y12 inhibitor with ASA) is generally given for six 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). However, debate is ongoing about the optimal duration of DAPT. Of note, patient characteristics may be an important factor in treatment duration decisions. In some settings, DAPT for 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, i.e., duration beyond 12 months (e.g., high risk of stent thrombosis and low risk of bleeding).

Current guidelines recommend tailoring the length of DAPT depending on patient characteristics. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend DAPT for six months following PCI for patients with stable coronary artery disease and for 12 months in patients with acute coronary syndrome (ACS), with the consideration of extended DAPT beyond 12 months if potential thrombotic risk is high and bleeding risk is deemed low. Particularly, the use of the DAPT score as a potential means of identifying high-risk patients was emphasized. Similarly, the European Society of Cardiology (ESC) updated guidelines in 2017 also support a one-year minimum duration of DAPT for patients with ACS. Recent Canadian guidelines support an individualized approach to selecting DAPT duration, with different recommendations for patients with ACS or non-ACS indications at the time of PCI.

Given the risk of developing stent thrombosis and de-novo recurrent ischemic events, evidence assessing the impact of extending the duration of DAPT beyond 12 months has been increasing during the last few years. Clinicians need to consider the potential benefits of extended DAPT alongside the associated bleeding risk to identify patients who are most likely to benefit. Also, in some jurisdictions, reimbursement of P2Y12 inhibitors after coronary stenting may be limited to 12 months, particularly reimbursement of prasugrel and ticagrelor. Accordingly, in 2018, CADTH undertook a systematic review of relevant randomized clinical trials (RCTs); a cost-utility analysis was also conducted to complement that work. Results from both assessments are available in a science report. Findings from this work were considered by the CADTH Canadian Drug Expert Committee (CDEC) to develop the recommendations that follow. The three P2Y12 inhibitors considered in these recommendations are described in Table 1.

Table 1: Drugs Included in the Science Report

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thienopyridines</td>
<td>Clopidogrel (Plavix, Sanofi-Aventis Canada)</td>
</tr>
<tr>
<td></td>
<td>Prasugrel (Effient, Eli Lilly Canada)</td>
</tr>
<tr>
<td>Adenosine diphosphate receptor antagonist</td>
<td>Ticagrelor (Brilinta, AstraZeneca)</td>
</tr>
</tbody>
</table>
CADTH Canadian Drug Expert Committee Values and Preferences

CDEC considered the available clinical and economic evidence, as presented in the CADTH science report. CDEC also considered feedback received from clinical experts to ensure that recommendations are clinically relevant. In developing these recommendations, CDEC placed a relatively high value on providing:

1. Optimal clinical outcomes for patients undergoing PCI, in particular, reducing the risk of recurrent vascular events following their procedure while not excessively increasing bleeding risk.
2. Cost-effective therapies for the Canadian health care system.

CDEC identified the values of safety and the efficient use of health care resources as being particularly important in making its recommendations for the optimal use of DAPT following PCI. CDEC noted that ensuring the efficient use of limited health care resources and promoting the sustainability of public drug programs is of great importance to Canadians.

Stakeholder Feedback

CDEC highly valued the input from stakeholders throughout the process of developing these recommendations. During the course of the project, stakeholders were invited to provide feedback on the list of included studies as well as the draft science report and the draft recommendations report. CADTH also invited patient groups to provide feedback on these documents.

Recommendations

Policy Question 1

Should P2Y12 inhibitors (i.e., clopidogrel, prasugrel, or ticagrelor) be reimbursed for use beyond 12 months in combination with ASA for patients who recently underwent PCI with bare-metal stent (BMS) or drug-eluting stent (DES) insertion?

Recommendation 1

CDEC recommends that a P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) be reimbursed for use beyond 12 months in combination with ASA in patients who recently underwent PCI with DES insertion.

Notes:

1. Any decision to extend DAPT beyond 12 months should be made together by patients and physicians to determine whether the potential benefit outweighs the risk factors based on individual patient characteristics, such as the risk of serious bleeding, and preferences.
2. Patients undergoing extended DAPT therapy should consult with their treating physician at least once per year to determine whether the extended DAPT therapy should continue.
3. The duration of extended DAPT treatment should not exceed three years beyond the initial 12 month period, unless recommended by a physician. The risks and benefits beyond three years are currently unknown.
4. Doses recommended in the 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use
of Antiplatelet Therapy for clopidogrel and prasugrel are the same for both standard and extended DAPT. For ticagrelor, however, while 90 mg twice daily is recommended for standard DAPT, a lower dose of 60 mg twice daily is recommended for extended DAPT.

Reasons for Recommendation
1. A systematic review of seven RCTs found that extending DAPT beyond 12 months is associated with a reduced risk of myocardial infarction (MI) (relative risk [RR] 0.58, 95% confidence interval [CI], 0.48 to 0.70; number needed to treat [NNT] 174) and probable or definite stent thrombosis (RR 0.38, 95% CI, 0.21 to 0.67; NNT 348) compared with standard DAPT (DAPT for six to 12 months). These results are mainly driven by clopidogrel because most patients enrolled in the included studies were using this P2Y12 inhibitor.

2. A systematic review of seven RCTs found that the use of extended DAPT is associated with an increased risk of bleeding, although the estimates of bleeding risk varied depending on the bleeding classification system used in the individual RCT. Data from two RCTs using the GUSTO classification system reported statistically significant increases in bleeding risks (GUSTO moderate bleeding RR 1.68, 95% CI, 1.22 to 2.30; number needed to harm [NNH] 156 and GUSTO moderate and severe bleeding RR 1.57, 95% CI, 1.17 to 2.11), compared with standard DAPT. These results are also mainly driven by clopidogrel because most patients enrolled in the included studies were using this P2Y12 inhibitor.

3. Because the duration of included studies extended to a maximum of 48 months, with the largest included study (i.e., the DAPT trial) following patients for up to 30 months, CDEC considers that extending DAPT beyond three years after an initial 12 months treatment should be undertaken only if the patient is evaluated by a physician with expertise in cardiovascular disease.

4. CDEC noted that the benefit versus risk ratio of DAPT for patients may vary over time and considers that patients should consult their cardiologist, or attending physician, on an annual basis to determine whether extended DAPT is still indicated for them.

5. A cost-utility analysis found that extended DAPT is either dominant or cost-effective compared with standard DAPT. Sensitivity analyses performed in the cost-utility analysis also suggested that the cost-effectiveness of DAPT varies depending on the P2Y12 inhibitor:
   - When clopidogrel comprises 100% of P2Y12 inhibitor use, extended DAPT is dominant
   - When prasugrel comprises 100% of P2Y12 inhibitor use, DAPT is cost-effective (incremental cost-utility ratio [ICUR] = $322/quality-adjusted life-year [QALY])
   - When ticagrelor comprises 100% of P2Y12 inhibitor use, DAPT is cost-effective (ICUR = $40,696/QALY) when the decision-maker’s willingness-to-pay is $50,000/QALY.

CDEC acknowledges that the above sensitivity analyses assume similar efficacy across P2Y12 inhibitors, which is a limitation of these analyses.

6. Subgroup analyses were associated with a number of limitations that limit the ability to draw strong inferences. In particular, sample sizes were small in the clinical evidence review and model assumptions were limiting the economic evidence review.
Discussion Points

- CDEC noted that patient selection needs to be highly individualized, which limits the ability to make strong group-level prescribing or listing recommendations. Also, there was limited evidence on subgroups in the science report. The latter also did not evaluate the role of scoring systems such as the DAPT score.

- Most of the studies included in the systematic review enrolled patients who underwent PCI with DES. Limited data were available for participants with an implanted BMS. CDEC noted that the limited availability of data on patients with implanted BMS prevents developing strong recommendations on the reimbursement of P2Y12 inhibitors beyond 12 months for this population. CDEC, however, acknowledges that reimbursement of P2Y12 inhibitors beyond 12 months in patients with implanted BMS may be considered when prescribed by a physician with expertise in cardiovascular disease who considered the individual characteristics and risk profile of each patient.

- Based on results from subgroup analyses and input from clinical experts, CDEC observed that patients presenting with ACS would appear to be more likely to derive benefits from extended DAPT, compared with patients with stable coronary artery disease. CDEC noted that the 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy has a strong recommendation supporting the use of extended DAPT in ACS patients who have lower bleeding risks. This update also includes a weak recommendation supporting the use of extended DAPT in non-ACS (i.e., stable coronary artery disease) patients with high-risk cardiovascular features and lower bleeding risks.

- CDEC noted that the 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy sets the maximum duration of extended DAPT to three years for most patients following PCI.

Policy Question 2
Which of the P2Y12 inhibitors (clopidogrel, prasugrel, or ticagrelor) should be reimbursed for use beyond 12 months in combination with ASA for patients who underwent PCI with BMS or DES insertion?

Recommendation 2
CDEC recommends that selection of which P2Y12 inhibitor is used for extended DAPT be made at the discretion of the treating physician and that this be based on the individual characteristics and risk profile of each patient.

Reasons for Recommendation

1. There is insufficient information about the comparative clinical effectiveness and cost-effectiveness of individual P2Y12 inhibitors (i.e., clopidogrel, prasugrel, and ticagrelor) to make any recommendation that differentiates among the individual P2Y12 inhibitors used with ASA beyond 12 months in patients who recently underwent PCI with BMS or DES insertion.
Discussion Point

Acknowledging limitations of the available evidence on P2Y12 inhibitors for extended DAPT, CDEC noted that current evidence does not support a cost premium of any one DAPT strategy over another. As such, evidence would support paying only the cost of the least expensive regimen for extended DAPT. CDEC, however, acknowledges that this approach could potentially result in a policy involving patients switching P2Y12 inhibitor after 12 months of DAPT, which is not clinically advisable, nor supported by any available evidence. Assessment of the clinical and cost-effectiveness of P2Y12 inhibitors for standard (six to 12 months) DAPT was outside the scope of this project.

Summary of the Evidence

Research Questions

There were four research questions of interest:

1. What is the comparative clinical efficacy and safety of shorter duration (six to 12 months) versus longer duration (i.e., >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 at time of PCI
   - Those with diabetes
   - Different age subgroups
   - Those who smoke?

2. What is the comparative cost-effectiveness of shorter duration (six to 12 months) versus longer duration (i.e., >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 at time of PCI
   - Those with diabetes
   - Different age subgroups
   - Those who smoke?

3. Compared with shorter treatment duration (six to 12 months), what is the comparative clinical efficacy and safety of ASA plus clopidogrel, prasugrel, or ticagrelor, when used for longer (i.e., >12 months) duration of DAPT following PCI with BMS or DES insertion in:
   - All post-PCI patients
   - Those with a prior MI
   - Those presenting with ACS at time of PCI
   - Those with diabetes
   - Different age subgroups
   - Those who smoke?
4. Compared with shorter treatment duration (six to 12 months), what is the comparative cost-effectiveness of ASA plus clopidogrel, prasugrel, or ticagrelor, when used for longer (i.e., > 12 months) duration of DAPT following PCI with BMS or DES insertion in:
   - All post-PCI patients
   - Those with a prior MI
   - Those presenting with ACS at time of PCI
   - Those with diabetes
   - Different age subgroups
   - Those who smoke?

Patient Considerations

CADTH did not receive any patient input for this project. Therefore, CDEC reviewed recent patient input received by CADTH previously for related therapies and coronary conditions. CDEC also considered information from a CADTH Rapid Response review of patient experiences and decisions regarding treatments for the secondary prevention of cardiovascular events. Based on this information, it seems that initially, the major concern for patients admitted into an emergency department or hospital for an MI or chest pain is averting death. If an invasive procedure (e.g., angioplasty with or without stent insertion) is required, then patients would like to lower their risk of excessive bleeding. Once the medical emergency is over, their focus shifts to lowering risk factors and preventing subsequent re-occurrences. Also, despite the compelling evidence supporting the use of cardiovascular medications in the secondary prevention of coronary artery disease, many patients discontinue treatment. Information considered by CDEC members during their deliberations suggested that the relationship between the patient and their clinicians can be complex, and can inadvertently contribute to poor outcomes in some cases.

Clinical Evidence

This section summarizes the clinical results (i.e., Research Questions 1 and 3). To address these questions a systematic review of RCTs was performed. This review assessed the benefits and harms associated with extending DAPT beyond 12 months, compared with DAPT for six to 12 months (standard DAPT). Trials were selected for inclusion if they involved adult participants who received standard DAPT or extended DAPT following PCI. The primary outcomes of the review are all-cause, cardiovascular, and non-cardiovascular death. Secondary outcomes are MI, stroke, stent thrombosis, urgent target vessel revascularization, MACCE, and bleeding (major, minor, and gastrointestinal). Subgroup data were obtained for clinically relevant patient subgroups (prior MI, ACS at presentation, diabetes, smokers, and aged more or less than 75 years).

Research Question 1

Overall, when considering data for all study participants of the seven included studies, extending DAPT beyond 12 months was associated with a reduced risk of MI (RR 0.58, 95% CI, 0.48 to 0.70; number needed to treat [NNT] 174) and probable or definite stent thrombosis (RR 0.38, 95% CI, 0.21 to 0.67; NNT 348), compared with DAPT for six to 12 months. These benefits were associated with an increased risk of bleeding (GUSTO moderate bleeding RR 1.68, 95% CI, 1.22 to 2.30; number needed to harm [NNH] 156), although the estimates of bleeding risk varied depending on the bleeding classification system used in the individual RCT. One large RCT (DAPT) reported a significant increase
in non-cardiovascular death (RR 2.15, 95% CI, 1.30 to 3.55) among participants who received DAPT for more than 12 months; however, no significant difference in risk was observed in two smaller trials (NIPPON\textsuperscript{12}, OPTIDUAL\textsuperscript{8}). These studies were deemed too heterogeneous to combine into a pooled estimate. Table 2 summarizes results for all end points for the whole population.

Table 2: Comparative Effect of Extended Versus Standard DAPT for the Whole Population

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DAPT &gt; 12 Months vs. DAPT 6 to 12 Months Relative Risk (95% CI)</th>
<th>No. of RCTs</th>
<th>No. of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>1.07 (0.80 to 1.42)</td>
<td>7</td>
<td>25,982</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.98 (0.74 to 1.30)</td>
<td>5</td>
<td>21,561</td>
</tr>
<tr>
<td>Non-cardiovascular death</td>
<td>2.15 (1.30 to 3.55)\textsuperscript{a}</td>
<td>3</td>
<td>14,666</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.58 (0.48 to 0.70)</td>
<td>6</td>
<td>24,534</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.94 (0.70 to 1.25)</td>
<td>6</td>
<td>24,534</td>
</tr>
<tr>
<td>Stent thrombosis: definite</td>
<td>0.49 (0.22 to 1.08)</td>
<td>5</td>
<td>20,825</td>
</tr>
<tr>
<td>Stent thrombosis: probable or definite</td>
<td>0.38 (0.21 to 0.67)</td>
<td>5</td>
<td>19,489</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>0.60 (0.24 to 1.54)</td>
<td>2</td>
<td>3,136</td>
</tr>
<tr>
<td>MACCE</td>
<td>0.95 (0.76 to 1.19)</td>
<td>5</td>
<td>21,227</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>0.89 (0.34 to 2.30)</td>
<td>1</td>
<td>3,773</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>1.42 (0.88 to 2.29)</td>
<td>4</td>
<td>9,579</td>
</tr>
<tr>
<td>TIMI minor bleeding</td>
<td>0.95 (0.53 to 1.72)</td>
<td>2</td>
<td>3,248</td>
</tr>
<tr>
<td>GUSTO moderate bleeding</td>
<td>1.68 (1.22 to 2.30)</td>
<td>2</td>
<td>13,046</td>
</tr>
<tr>
<td>GUSTO severe bleeding</td>
<td>1.41 (0.90 to 2.20)</td>
<td>2</td>
<td>13,046</td>
</tr>
<tr>
<td>GUSTO moderate or severe bleeding</td>
<td>1.57 (1.17 to 2.11)</td>
<td>2</td>
<td>13,046</td>
</tr>
<tr>
<td>BARC Type 3 bleeding</td>
<td>1.29 (0.76 to 2.22)</td>
<td>3</td>
<td>16,353</td>
</tr>
<tr>
<td>BARC Type 5 bleeding</td>
<td>1.72 (0.62 to 4.47)</td>
<td>3</td>
<td>16,353</td>
</tr>
<tr>
<td>BARC Type 2,3,5 bleeding</td>
<td>0.89 (0.48 to 1.68)</td>
<td>1</td>
<td>1,398</td>
</tr>
</tbody>
</table>

RCT = randomized clinical trials.

\textsuperscript{a} Finding from the DAPT trial: increased risk of non-cardiovascular death among patients who received extended DAPT. Two smaller RCTs (OPTIDUAL, NIPPON) reported no significant difference between DAPT durations.

Most of the included studies enrolled participants who underwent PCI with DES. As such, the findings for this subgroup were similar to the reference case involving all participants. Two RCTs (DAPT\textsuperscript{11}, PRODIGY\textsuperscript{10}) included a small proportion of participants with an implanted BMS (15% to 25%), and data were not reported for all the outcomes of interest. The available data for participants with a BMS suggest that there are no statistically significant differences between DAPT durations in the risk of all-cause death, cardiovascular death, MI, stroke, definite stent thrombosis, definite or probable stent thrombosis, or MACCE. Data suggest an increased risk of BARC Types 2 and 3 bleeding with DAPT for more than 12 months. No data were available for non-cardiovascular death, urgent revascularization, or gastrointestinal bleeding among participants with an implanted BMS. These findings were based on a small number of participants with a BMS (n = 2,179) and should be interpreted with caution.
Table 3 summarizes efficacy results obtained from statistically pooled estimates for the subgroups of interest. Results obtained from individual RCTs, including situations in which more than one RCT had been retrieved but statistical pooling was not possible, are not reported here due to the high volume of such information. Accordingly, Table 3 may not reflect the full range of results for subgroups; readers interested in this information are referred to the science report. Results in Table 3 are presented for combined DES and BMS patients with the exception of the analyses based on smoking status, which are based on patients with implanted DES. Given there are a number of limitations associated with these analyses, CDEC mainly considered the whole population in developing their recommendations.

**Table 3: Comparative Effect of Extended Versus Standard DAPT: Subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>All-cause death RR (95% CI)</th>
<th>CVD RR (95% CI)</th>
<th>Non-CVD RR (95% CI)</th>
<th>MI RR (95% CI)</th>
<th>Stroke RR (95% CI)</th>
<th>Definite ST RR (95% CI)</th>
<th>Probable or definite ST, RR (95% CI)</th>
<th>Urgent revasc. RR (95% CI)</th>
<th>MACCE RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>1.04 (0.72 to 1.51)</td>
<td>0.52 (0.05 to 5.69)</td>
<td>NA</td>
<td>0.48 (0.36 to 0.64)</td>
<td>0.77 (0.42 to 1.39)</td>
<td>NA</td>
<td>0.29 (0.16 to 0.52)</td>
<td>0.35 (0.04 to 3.30)</td>
<td>0.67 (0.53 to 0.83)</td>
</tr>
<tr>
<td>No prior MI</td>
<td>1.64 (1.08 to 2.48)</td>
<td>NA</td>
<td>NA</td>
<td>0.63 (0.46 to 0.87)</td>
<td>0.90 (0.52 to 1.53)</td>
<td>NA</td>
<td>0.32 (0.15 to 0.68)</td>
<td>NA</td>
<td>0.87 (0.69 to 1.10)</td>
</tr>
<tr>
<td>ACS</td>
<td>1.20 (0.51 to 2.83)</td>
<td>0.66 (0.11 to 3.91)</td>
<td>NA</td>
<td>0.49 (0.29 to 0.85)</td>
<td>1.06 (0.49 to 2.32)</td>
<td>NA</td>
<td>0.26 (0.12 to 0.54)</td>
<td>0.08 (0.00 to 1.34)</td>
<td>No pooled estimate</td>
</tr>
<tr>
<td>No ACS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>No pooled estimate</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.27 (0.86 to 1.89)</td>
<td>1.02 (0.61 to 1.71)</td>
<td>1.71 (0.79 to 3.70)</td>
<td>0.74 (0.54 to 1.02)</td>
<td>1.01 (0.52 to 1.95)</td>
<td>0.41 (0.16 to 1.06)</td>
<td>0.48 (0.21 to 1.06)</td>
<td>0.96 (0.20 to 4.74)</td>
<td>No pooled estimate</td>
</tr>
<tr>
<td>No diabetes</td>
<td>1.24 (0.86 to 1.80)</td>
<td>NA</td>
<td>NA</td>
<td>0.44 (0.33 to 0.59)</td>
<td>NA</td>
<td>NA</td>
<td>0.29 (0.17 to 0.50)</td>
<td>NA</td>
<td>No pooled estimate</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>1.32 (0.39 to 4.54)</td>
<td>0.98 (0.24 to 4.04)</td>
<td>NA</td>
<td>1.48 (0.63 to 3.47)</td>
<td>8.59 (1.08 to 68.28)</td>
<td>0.54 (0.05 to 5.89)</td>
<td>0.72 (0.20 to 2.51)</td>
<td>0.91 (0.06 to 14.32)</td>
<td>No pooled estimate</td>
</tr>
<tr>
<td>&lt; 75 years</td>
<td>1.64 (0.76 to 3.56)</td>
<td>2.41 (0.47 to 12.39)</td>
<td>NA</td>
<td>1.07 (0.44 to 2.62)</td>
<td>2.89 (0.79 to 10.64)</td>
<td>0.96 (0.24 to 3.84)</td>
<td>0.96 (0.24 to 3.84)</td>
<td>NA</td>
<td>No pooled estimate</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.90a (0.42 to 1.92)</td>
<td>NA</td>
<td>N/A</td>
<td>0.38 (0.24 to 0.60)</td>
<td>NA</td>
<td>NA</td>
<td>0.20 (0.09 to 0.49)</td>
<td>N/A</td>
<td>0.69 (0.52 to 0.91)</td>
</tr>
<tr>
<td>No smoking</td>
<td>0.99a (0.67 to 1.47)</td>
<td>NA</td>
<td>NA</td>
<td>0.55 (0.41 to 0.72)</td>
<td>NA</td>
<td>NA</td>
<td>0.36 (0.19 to 0.67)</td>
<td>N/A</td>
<td>0.87 (0.64 to 1.20)</td>
</tr>
</tbody>
</table>

CVD = cardiovascular death; CI = confidence interval; MACCE = major adverse cardiac and cerebrovascular event; MI = myocardial infarction; NA = not available; RR = relative risk; ST = stent thrombosis; revasc = revascularization.

* Results presented as hazard ratio.
Bleeding risk was also considered by CDEC in developing their recommendations. However, as for the efficacy results, given the limitations associated with these subgroup analyses, CDEC mainly considered results for the whole population in developing their recommendations. The following section summarizes key bleeding risks for the subgroups.

**Participants With a Prior MI**

Among participants with a prior MI, the risk of GUSTO moderate or severe bleeding, GUSTO moderate bleeding, and BARC Type 2, 3 or 5 bleeding was significantly higher among those who received extended DAPT compared with DAPT for six to 12 months either with or without a history of MI. There was no difference in GUSTO severe bleeding between DAPT durations for either those with or those without a history of MI (Table 4).

**Table 4: Bleeding Reported by MI History**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Bleeding Classification System</th>
<th>Prior MI</th>
<th></th>
<th>RR (95% CI)</th>
<th>No Prior MI</th>
<th></th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mauri 2014 (DAPT)</td>
<td>GUSTO moderate or severe</td>
<td>12 mo: 29/2,625, 30 mo: 57/2,715</td>
<td>1.89 (1.21 to 2.95)</td>
<td>12 mo: 54/3,161, 30 mo: 85/3,147</td>
<td>1.58 (1.13 to 2.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GUSTO moderate</td>
<td>12 mo: 16/2,625, 30 mo: 38/2,715</td>
<td>2.30 (1.28 to 4.11)</td>
<td>12 mo: 38/3,161, 30 mo: 57/3,147</td>
<td>1.51 (1.00 to 2.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GUSTO severe</td>
<td>12 mo: 13/2,625, 30 mo: 16/2,715</td>
<td>1.19 (0.57 to 2.47)</td>
<td>12 mo: 19/3,161, 30 mo: 28/3,147</td>
<td>1.48 (0.83 to 2.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BARC Type 2,3 or 5</td>
<td>12 mo: 55/2,625, 30 mo: 117/2,715</td>
<td>2.06 (1.50 to 2.82)</td>
<td>12 mo: 101/3,161, 30 mo: 192/3,147</td>
<td>1.91 (1.51 to 2.42)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; MI = myocardial infarction; mo = months; RR = relative risk.

**Participants With ACS at Presentation**

Among participants with ACS at presentation, extended DAPT was associated with a significantly higher risk of BARC Type 2, 3, or 5 bleeding, GUSTO moderate or severe bleeding, and GUSTO moderate bleeding, but no statistically significant difference in GUSTO severe bleeding (Table 5). No data were available for participants without ACS.

**Table 5: Bleeding Reported by ACS Status at Presentation**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Bleeding Classification System</th>
<th>ACS</th>
<th></th>
<th>RR (95% CI)</th>
<th>No ACS</th>
<th></th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mauri 2014 (DAPT)</td>
<td>GUSTO moderate or severe</td>
<td>12 mo: 14/1,771, 30 mo: 34/1,805</td>
<td>2.38 (1.28 to 4.42)</td>
<td>NR</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GUSTO moderate</td>
<td>12 mo: 5/1,771, 30 mo: 22/1,805</td>
<td>4.23 (1.64 to 11.37)</td>
<td>NR</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GUSTO severe</td>
<td>12 mo: 9/1,771, 30 mo: 13/1,805</td>
<td>1.42 (0.61 to 3.31)</td>
<td>NR</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BARC Type 2,3,5</td>
<td>12 mo: 37/1,771, 30 mo: 78/1,805</td>
<td>2.07 (1.41 to 3.04)</td>
<td>NR</td>
<td>—</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; CI = confidence interval; mo = months; NR = not reported; RR = relative risk.
Participants With Diabetes

Among participants with diabetes, extended DAPT was associated with a significantly higher risk of BARC Type 2, 3, or 5 bleeding as well as BARC Type 3 bleeding. Among those with no diabetes, there was a significant increase in the risk of GUSTO moderate or severe bleeding associated with extended DAPT (Table 6).

Table 6: Bleeding Among Participants With or Without Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Bleeding Classification System</th>
<th>Diabetes</th>
<th>No Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. Events/No. Participants</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Mauri 2014 (DAPT)</td>
<td>GUSTO moderate or severe</td>
<td>12 mo: 26/1,654 30 mo: 41/1,737</td>
<td>1.50 (0.92 to 2.44)</td>
</tr>
<tr>
<td></td>
<td>GUSTO moderate</td>
<td>12 mo: 20/1,654 30 mo: 32/1,737</td>
<td>1.52 (0.87 to 2.65)</td>
</tr>
<tr>
<td></td>
<td>GUSTO severe</td>
<td>12 mo: 6/1,654 30 mo: 9/1,737</td>
<td>1.43 (0.51 to 4.00)</td>
</tr>
<tr>
<td></td>
<td>BARC Type 2,3,5</td>
<td>12 mo: 57/1,654 30 mo: 95/1,737</td>
<td>1.59 (1.15 to 2.19)</td>
</tr>
<tr>
<td></td>
<td>BARC Type 3</td>
<td>12 mo: 24/1,654 30 mo: 44/1,737</td>
<td>1.75 (1.07 to 2.86)</td>
</tr>
<tr>
<td></td>
<td>BARC Type 5</td>
<td>12 mo: 2/1,654 30 mo: 1/1,737</td>
<td>0.48 (0.04 to 5.25)</td>
</tr>
</tbody>
</table>

CI = confidence interval; MI = myocardial infarction; mo = months; NR = not reported; RR = relative risk.

Age Groups

Among participants who were at least 75 years old, extended DAPT was associated with a significantly higher risk of BARC Type 2, 3, 5 bleeding, BARC Type 3, 5 bleeding, and GUSTO moderate or severe bleeding. Among those younger than 75 years, there was a significant increase in the risk of BARC Type 2, 3, 5 bleeding (Table 7).

Table 7: Bleeding Reported by Age Group

<table>
<thead>
<tr>
<th>Trial</th>
<th>Bleeding Classification System</th>
<th>≥ 75 years</th>
<th>&lt; 75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. Events/No. Participants</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Valgimigli 2012 (PRODIGY)</td>
<td>BARC Type 2,3,5</td>
<td>6 mo: 9/304 24 mo: 23/283</td>
<td>2.75 (1.29 to 5.83)</td>
</tr>
<tr>
<td></td>
<td>BARC Type 3,5</td>
<td>6 mo: 5/304 24 mo: 14/283</td>
<td>3.01 (1.10 to 8.24)</td>
</tr>
<tr>
<td></td>
<td>BARC Type 3</td>
<td>6 mo: 4/304 24 mo: 9/283</td>
<td>2.42 (0.75 to 7.76)</td>
</tr>
<tr>
<td></td>
<td>GUSTO moderate or severe</td>
<td>6 mo: 3/304 24 mo: 14/283</td>
<td>5.01 (1.46 to 17.26)</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; mo = months; RR = relative risk.
Participants Who Smoke

By use of either the GUSTO (moderate or severe) or BARC (Type 2, 3, 5) bleeding classification, the risk of bleeding was increased among non-smokers who received DAPT for >12 months compared with DAPT for six to 12 months. Among smokers, there was no significant difference in the risk of bleeding between DAPT durations by use of either classification system (Table 8).

Table 8: Bleeding Reported by Smoking Status

<table>
<thead>
<tr>
<th>Trial</th>
<th>Smoking Classification System</th>
<th>No. Events/No. Participants</th>
<th>RR (95% CI)</th>
<th>No. Events/No. Participants</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valgimigli 2012 (PRODIGY)</td>
<td>BARC Type 2,3,5</td>
<td>6 mo: 10/247, 24 mo: 12/222</td>
<td>1.34 (0.59 to 3.03)</td>
<td>6 mo: 24/731, 24 mo: 61/762</td>
<td>2.44 (1.54 to 3.87)</td>
</tr>
<tr>
<td>Mauri 2014 (DAPT)</td>
<td>GUSTO moderate or severe</td>
<td>12 mo: 17/1,210, 30 mo: 15/1,222</td>
<td>0.87 (0.44 to 1.74)</td>
<td>12 mo: 56/3,683, 30 mo: 104/3,743</td>
<td>1.83 (1.32 to 2.52)</td>
</tr>
</tbody>
</table>

CI = confidence interval; mo = months; RR = relative risk.

Research Question 3

The evidence base for this research question was the same as for Research Question 1 and included data from seven RCTs,6-12 representing the treatment period starting six months after PCI. Clopidogrel was the most commonly used P2Y12 inhibitor in the included RCTs. Three RCTs (OPTIDUAL,6 DES-LATE,6 PRODIGY10) involved only clopidogrel, while the remaining RCTs included more than one P2Y12 inhibitor. Of the RCTs that involved more than one P2Y12 inhibitor, clopidogrel was the predominant P2Y12 inhibitor used. The available data are summarized below for each P2Y12 inhibitor.

Clopidogrel

The RCTs that were used to address Research Question 1 primarily involved use of clopidogrel, with between 65% and 100% of participants receiving this antiplatelet drug. Because the findings of the base case were driven primarily by clopidogrel, no additional analyses were performed to address Research Question 3.

Prasugrel

Four of the included RCTs involved prasugrel (ITALIC,7 DAPT,11 ARCTIC-Interuption,6 NIPPON15), with use by 0.1% to 35% of participants. Of these, one RCT (DAPT11) provided subgroup data for participants who received prasugrel. Data from the DAPT trial were available for the following outcomes:

- MI: among participants who received prasugrel, extended DAPT was associated with a lower risk of MI compared with those who received standard DAPT (RR 0.36, 95% CI, 0.24 to 0.53).

- Stent thrombosis:
  - Definite thrombosis: no data were reported for definite stent thrombosis among participants taking prasugrel.
  - Definite or probable stent thrombosis: among participants who received prasugrel, extended DAPT was associated with a lower risk of definite or probable stent thrombosis compared with those who received standard DAPT (RR 0.26, 95% CI, 0.13 to 0.52).
• MACCE: among participants who received prasugrel, extended DAPT was associated with a lower risk of MACCE compared with those who received standard DAPT (RR 0.55, 95% CI, 0.41 to 0.74).

• GUSTO moderate or severe bleeding: among participants who received prasugrel, extended DAPT was associated with a higher risk of GUSTO moderate or severe bleeding compared with those who received standard DAPT (RR 1.69, 95% CI, 1.01 to 2.85).

No data were reported for all-cause death, cardiovascular death, non-cardiovascular death, stroke, urgent revascularization, or TIMI bleeding.

Ticagrelor

Of the included RCTs, ticagrelor was an eligible P2Y12 inhibitor in one RCT (ITALIC7); however, no participants in the 24 month DAPT group and 0.1% of participants in the six month DAPT group received ticagrelor. As such, there was insufficient data available to assess the comparative benefits and harms of extended versus standard DAPT involving ticagrelor.

One large RCT (PEGASUS-TIMI 5413) involving participants with a prior MI was identified during the review; however, this RCT did not meet the eligibility criteria for inclusion in this review. Participants in the PEGASUS-TIMI 54 trial were randomized to ticagrelor 60 mg or 90 mg twice daily or placebo one to three years after a MI (median 1.7, interquartile range 1.2 to 2.3 years). About 83% of participants had undergone stenting, with 39% receiving a DES and 41% receiving a BMS. After PCI, participants received a P2Y12 inhibitor at the discretion of their treating physician, and the percentage of participants who received a P2Y12 inhibitor was not reported. Because of uncertainty about whether all participants received a P2Y12 inhibitor, and because the duration of potential DAPT before randomization was longer than the eligibility criteria for the current review (i.e., six to 12 months following PCI), this RCT was not eligible for inclusion. However, because this trial represents the only identified RCT to assess the benefits and harms of long-term ticagrelor use, results were summarized and made available as supplemental information to CDEC during their deliberations (Appendix 1).

Overall, given that most RCTs included in the clinical review enrolled participants who received clopidogrel as part of the DAPT regimen, it was not possible for CDEC to determine whether the choice of P2Y12 inhibitor impacts the effect of extending DAPT beyond 12 months.

Economic Evidence

This section summarizes the economic results, that is, Research Questions 2 and 4. To address these questions, CADTH built an economic model assessing the costs and health outcomes associated with the administration of DAPT for more than 12 months (extended DAPT group) versus the use of ASA alone after an initial six to 12 months treatment period with DAPT (six to 12 months of DAPT group). The analysis was in the form of a cost-utility analysis. The results of the CADTH clinical evaluation and meta-analysis were used to inform the clinical efficacy and safety outcomes in the model. The medical literature was used to supplement CADTH meta-analysis, in particular for long-term outcomes, utilities, and costs (when costs could not be found directly from Canadian sources). The perspective of the cost-utility analysis was that of the Canadian public health care payer. To replicate the results from the clinical studies and forecast the clinical effects over a longer time horizon, a Markov cohort model was built. Of note, in Research Question 2, the base case assessed
DAPT as a therapeutic intervention on its own. P2Y12 inhibitor specific analyses were originally planned to address Research Question 4. In view of the limited clinical data available, economic analyses to answer Research Question 4 could not, however, be performed. The economic evaluation therefore focused on Research Question 2.

Research Question 2

According to the base-case analysis, extended DAPT is dominant (i.e., more effective and less costly) compared with the six to 12 months DAPT strategy. Both lifetime incremental benefit, (0.0160 QALY) and savings ($707) are small (Table 9). This dominance was observed in 71.6% of the 5,000 iterations, while extended DAPT was dominated (i.e., less effective and more expensive than six to 12 month of DAPT) in only 1.5% of the iterations, and in 13.8% of iterations the ICUR was above $50,000 per QALY.

The incremental benefits associated with extended DAPT were largely realized (98%) from the lifetime analysis. When the analysis was limited to the duration of the trials included in CADTH meta-analysis (i.e., average of 19 months beyond the initial six to 12 month of DAPT), the incremental benefit of extended DAPT was only 0.0003 QALYs with incremental costs of $161, resulting in an ICUR of $546,427 per QALY. Uncertainty exists regarding the impact of extended DAPT beyond the duration of studies included in the CADTH meta-analysis (i.e., three to four years). For this reason, scenario analyses were performed to address the uncertainty in the post-extended DAPT phase of the model as well as the uncertainty related to some inputs (Table 9). In most scenario analyses, extended DAPT remained dominant, that is, more effective and less costly. However, in four scenarios, the ICUR was above $25,000 per QALY. This was observed when ticagrelor was assumed to be the sole P2Y12 inhibitor used in the DAPT regimen, when the analysis was performed on a shorter time horizon (i.e., 19 months beyond the initial six to 12 months DAPT), as well as when using efficacy and safety from studies with an extended DAPT duration of 24 to 30 months and 36 to 48 months.

Analyses conducted in patient subgroups were considered as exploratory because the data to inform these analyses were obtained from few studies (i.e., one or two) and required additional assumptions to be made. These exploratory analyses indicated that extended DAPT was dominant (i.e., more effective and less costly) in patients with a prior MI and those presenting with ACS. In patients younger than 75 years of age, the ICUR was $37,901 per QALY. 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, and thus may not be the preferred option in these patients (Table 9).
Table 9: Key Results of the Economic Analysis

<table>
<thead>
<tr>
<th>Scenario</th>
<th>6 to 12 Months Of DAPT</th>
<th>Extended DAPT</th>
<th>Incremental (Versus Extended DAPT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Costs</td>
<td>QALY</td>
<td>Costs</td>
</tr>
<tr>
<td>Base case</td>
<td>$40,227</td>
<td>13.64</td>
<td>$39,520</td>
</tr>
<tr>
<td>Alternative proportion for antiplatelet drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) 100% clopidogrel</td>
<td>$40,233</td>
<td>13.63</td>
<td>$39,340</td>
</tr>
<tr>
<td>b) 100% prasugrel</td>
<td>$40,319</td>
<td>13.64</td>
<td>$40,324</td>
</tr>
<tr>
<td>c) 100% ticagrelor</td>
<td>$40,243</td>
<td>13.63</td>
<td>$40,895</td>
</tr>
<tr>
<td>Shorter time horizon (19 months)</td>
<td>$787</td>
<td>1.23</td>
<td>$947</td>
</tr>
<tr>
<td>No CV event (i.e., MI, stroke, etc.) post-extended DAPT treatment</td>
<td>$5,929</td>
<td>14.65</td>
<td>$5,225</td>
</tr>
<tr>
<td>DAPT duration in control: 6 months</td>
<td>$29,562</td>
<td>14.06</td>
<td>$29,640</td>
</tr>
<tr>
<td>DAPT duration in control: 12 months</td>
<td>$43,589</td>
<td>13.49</td>
<td>$42,336</td>
</tr>
<tr>
<td>Extended DAPT duration: 18 months</td>
<td>$29,033</td>
<td>14.11</td>
<td>$28,912</td>
</tr>
<tr>
<td>Extended DAPT duration: 24 to 30 months</td>
<td>$45,840</td>
<td>13.42</td>
<td>$44,904</td>
</tr>
<tr>
<td>Extended DAPT duration: 36 to 48 months</td>
<td>$30,904</td>
<td>14.02</td>
<td>$30,448</td>
</tr>
<tr>
<td>Rebound effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Maximal rebound at 3 months</td>
<td>$40,157</td>
<td>13.64</td>
<td>$39,737</td>
</tr>
<tr>
<td>b) Rates reaching control rates at 6 months</td>
<td>$40,214</td>
<td>13.63</td>
<td>$40,171</td>
</tr>
<tr>
<td>Exploratory subgroup analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>$56,045</td>
<td>12.94</td>
<td>$53,936</td>
</tr>
<tr>
<td>No prior MI</td>
<td>$46,773</td>
<td>13.48</td>
<td>$45,697</td>
</tr>
<tr>
<td>ACS</td>
<td>$48,826</td>
<td>13.17</td>
<td>$47,229</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$51,880</td>
<td>13.14</td>
<td>$51,749</td>
</tr>
<tr>
<td>No diabetes</td>
<td>$45,525</td>
<td>13.41</td>
<td>$44,239</td>
</tr>
<tr>
<td>Above 75 years old</td>
<td>$9,596</td>
<td>6.51</td>
<td>$14,491</td>
</tr>
<tr>
<td>Below 75 years old</td>
<td>$33,016</td>
<td>14.10</td>
<td>$37,406</td>
</tr>
</tbody>
</table>

QALY = quality-adjusted life-year; ΔCosts = incremental costs; ΔQALY = incremental QALY; DAPT = dual antiplatelet therapy; CV = cardiovascular; MI = myocardial infarction.
Research Question 4

As previously stated, economic analyses to answer Research Question 4 could not be performed given the limited comparative clinical data available on the different P2Y12 inhibitors.

Discussion

Clinical Evidence

Extending DAPT beyond 12 months may reduce the risk of MI and stent thrombosis, but may also increase the risk of bleeding. There were no significant differences in the risk of all-cause or cardiovascular death, stroke, urgent target revascularization, MACCE, or gastrointestinal bleeding between extended and standard DAPT. Results were similar among the subset of participants with an implanted DES; however, limited data were available for participants with an implanted BMS. One large RCT (DAPT trial) reported an increased risk of non-cardiovascular death among participants who received extended DAPT; however, this finding was not replicated in two smaller RCTs.

Findings from subgroup analyses that focused on clinically important patient characteristics suggest that patients who have experienced a prior MI, those with ACS at presentation, as well as patients without diabetes, or younger than 75 years may derive the most benefit from extended DAPT. As such, individualized risk assessments should be made to determine the optimal duration of DAPT. Limited data were available for some subgroups, limiting the power of these analyses to detect differences between DAPT durations. The majority of subgroup data were obtained from one RCT (the DAPT trial). Randomization may not hold in the subgroups, potentially leading to imbalances between the treatment groups. As well, the small number of participants in some subgroups may increase the probability of a false-negative finding. It should be noted that a statistically non-significant finding does not preclude a potentially clinically important finding. Because of these limitations, the results of the subgroup analyses should be interpreted with caution.

In 2014, the US Food and Drug Administration (FDA) issued a Safety Communication concerning the increased risk of death observed in the DAPT trial. In this study, participants who received 30 months of DAPT were at higher risk of death compared with those who received 12 months of DAPT. Specifically, the DAPT study reported an increased risk of all-cause death among those who received extended DAPT. The higher rate of death was largely explained by an increase in deaths from non-cardiovascular causes, primarily cancer and trauma deaths. The increased risk of death with longer DAPT was seen in the patients given clopidogrel, but not those given prasugrel. In 2015, the FDA issued an update to their 2014 Safety Communication stating that, in their meta-analysis involving the DAPT trial and “other long-term clinical trials,” they had found no increased risk of all-cause death with extended DAPT (i.e., DAPT for more than 12 months) compared with short-term (i.e., DAPT of six months or less) DAPT. Also, a patient-level meta-analysis of cardiovascular trials assessing the impact of continued clopidogrel use on mortality and cancer was published in 2018. While results indicate that prolonged clopidogrel therapy has no overall effect on mortality or cancer, they also indicate that such therapy reduces ischemic events, including MI and stroke, but also increases rates of bleeding, including a 0.12% absolute increase in fatal bleeding (P = 0.03). It should be noted however that this meta-analysis was interested in a more diverse cardiovascular population than the CADTH clinical review. Indeed, while the 2018 patient-level meta-analysis included three trials that enrolled patients with coronary artery disease after PCI or ACS, including patients on
clopidogrel from the DAPT trial, it also included one trial of patients with recent lacunar stroke, one trial of patients at high risk of atherothrombotic events and one trial of patients with atrial fibrillation. Of interest, while it is reassuring that no increase in mortality was observed, results of this meta-analysis do however raise potential questions on the net health impact of prolonged clopidogrel therapy when accounting for the competing effects of this drug on ischemic and bleeding events.\textsuperscript{16}

In the CADTH clinical review, most of the included trials involved use of clopidogrel as the P2Y12 inhibitor associated with ASA, and limited subgroup data were available for prasugrel and none for ticagrelor. As such, the findings of this review mainly apply to clopidogrel. Given that clopidogrel is still currently widely used after PCI, these findings are nonetheless important for clinicians looking to optimize the care of their patients who have undergone PCI. The findings are also relevant to the policy questions of this review. There is a need to understand whether reimbursement policies for thromboembolic prophylaxis with P2Y12 inhibitors (as part of DAPT regimens) initiated after PCI should accommodate renewal of the reimbursement of the P2Y12 inhibitor for a period extending beyond the first 12 months.

Given the lack of data on ticagrelor in the clinical systematic review, which prevented addressing Policy Question 2, CDEC considered findings of the PEGASUS-TIMI 54 trial,\textsuperscript{13} which randomized participants to receive ticagrelor or placebo. As previously stated, this study did not meet the eligibility criteria for the CADTH clinical review, due to some differences in the population and intervention versus those of the included studies, but the results may nonetheless inform clinical and policy decisions. As such, CDEC acknowledges that reimbursement of ticagrelor at a dose of 60 mg twice daily to patients with a previous MI (as opposed to the currently indicated 90 mg twice daily post-ACS prophylaxis) is a clinically related policy question to those considered in this report. Importantly, the 60 mg dose of ticagrelor in the PEGASUS-TIMI 54 trial reduced the rate of this trial’s primary efficacy endpoint (i.e., a composite of cardiovascular death, MI, or stroke). This is reflected in their 2016 listing recommendation for ticagrelor 60 mg which, among other criteria or condition, involves meeting the inclusion criteria of the PEGASUS-TIMI 54 trial in order to obtain reimbursement for this secondary prevention regimen for up to three years.\textsuperscript{17} More specifically, patients need to meet the following criteria:

- Patients who are between 12 and 24 months from their most recent MI, and less than 12 months since dual antiplatelet coverage with ASA and an adenosine diphosphate receptor inhibitor, with a high risk of subsequent cardiovascular events, defined as requiring at least one of:
  - age of 65 years or greater
  - diabetes requiring medication
  - second prior spontaneous MI (more than one year ago)
  - angiographic evidence of multivessel coronary artery disease
  - chronic renal dysfunction (defined as creatinine clearance < 60 mL/min).\textsuperscript{17}

The 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of Guidelines for the Use of Antiplatelet Therapy includes a DAPT regimen of ASA 81 mg daily and ticagrelor 60 mg twice daily up to three years as an option in patients with ACS who tolerate one year of DAPT without a major bleeding event and who are not at high risk of bleeding. Other P2Y12 options for extended therapy mentioned in the Canadian guidelines include clopidogrel 75 mg daily or prasugrel 10 mg once daily. In their recommendation, the first year of DAPT must involve use of ASA 81 mg...
daily with either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily or clopidogrel 75 mg daily.  

Economic Evaluation

The economic analyses showed that, when considering the estimated lifetime impacts, extending DAPT beyond the initial six to 12 months is a dominant option, i.e., generating a small incremental benefit (i.e., 0.0160 QALY) and small savings (i.e., $707). However, 98% of this benefit was accrued in the post-extended DAPT phase of the model.

In the economic analysis, it is uncertain whether the impact of extended DAPT will remain once treatment ends. The duration of the included studies extended to a maximum of 48 months. Also, information on rates of event after end of treatment was only available from one study and for three months only. Several assumptions needed to be made on the risk of events (e.g., death post-MI or stroke, second MI or stroke, etc.), in particular in the post-extended DAPT phase of the model. As 98% of extended DAPT incremental benefit came from the post-extended DAPT phase of the model, it is possible that using other assumptions or inputs for this phase of the model could have led to different results. Several scenarios were designed to address this uncertainty and resulted in conclusions similar to that of the base case except in four cases. These were when ticagrelor was the sole P2Y12 inhibitor in the DAPT regimen (assuming that clinical impact is the same across the three antiplatelet drugs), when extended DAPT duration was 24 to 30 months or 36 to 48 months, and when the analysis was limited to the duration of the trials included in CADTH meta-analysis.

In the economic evaluation, analyses per patient subgroups should only be considered as exploratory as data to inform these analyses were coming from only one or two studies and required additional assumptions to be made. Exploratory subgroup analyses indicate that extended DAPT is more effective and less costly; hence, would be the preferred option in patients who had a prior MI and those presenting with ACS. Extended DAPT is less effective and also less costly (ICUR below $18,706 per QALY) in patients with diabetes and patients with no prior MI. In patients older than 75 years of age, extended DAPT is less effective and more costly than six to 12 months of DAPT (i.e., six to 12 months DAPT is dominant). In patients younger than 75 years of age, extended DAPT is more effective and more costly with an ICUR of $37,901 per QALY. However, more evidence would be required to provide more robust conclusions.

November 20, 2018 Meeting — Committee Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh V. Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Note: Two external clinical experts who are practising as interventional cardiologists participated in the discussion, but did not vote on the recommendations.

Regrets

Dr. Alun Edwards
Conflicts of Interest
None

January 15, 2019 Meeting — Committee Members
Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh V. Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Regrets
None

Conflicts of Interest
None
References


Appendix 1: Use of Ticagrelor in the PEGASUS-TIMI 54 Trial

The PEGASUS-TIMI 54\textsuperscript{13} RCT involved participants in 31 countries with a prior MI one to three years before enrolment (median 1.7, interquartile range [1.2 to 2.3]) years. Participants were aged at least 50 years and had at least one other high-risk feature (> 65 years, diabetes, second prior MI, multivessel coronary artery disease, chronic renal dysfunction). In total, 83% of participants underwent stenting. About 17% of participants had more than one prior MI, and about 54% of these were ST-elevation myocardial infarction (STEMI).

At study enrolment, all participants were taking ASA 75 mg to 100 mg once daily. The use of P2Y12 inhibitors before enrolment was at the discretion of the treating physician, and the percentage of participants who received a P2Y12 inhibitor was not reported. Because of uncertainty about whether all participants received a P2Y12 inhibitor, and because the duration of potential DAPT before randomization was longer than the eligibility criteria (six to 12 months), the PEGASUS-TIMI 54\textsuperscript{13} RCT was not eligible for inclusion in the current systematic review.

Participants in PEGASUS-TIMI 54\textsuperscript{13} were randomized to ticagrelor 60 mg or 90 mg twice daily or placebo (n = 21,162) and were followed for a median of 33 months (IQR 28 to 37 months). The primary efficacy outcome was a composite of cardiovascular death, MI, or stroke. The primary safety outcome was TIMI major bleeding.

Among all participants (with or without PCI), both ticagrelor 60 mg and 90 mg twice daily reduced the primary outcome (cardiovascular death, MI, or stroke) relative to 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), with the outcome experienced by 7.85% among participants who received 90 mg ticagrelor, 7.77% among those who received 60 mg, and 9.04% in the placebo group in three-year Kaplan-Meier analysis.\textsuperscript{13}

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).\textsuperscript{13} Premature discontinuations of treatment were 32.0%, 28.7%, and 21.4% in ticagrelor 90 mg, 60 mg and placebo group, respectively, mainly due to adverse events in the two ticagrelor groups.

Among participants who had prior PCI, the risk of the primary outcome (cardiovascular death, MI, or stroke) 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).\textsuperscript{13}