Common Drug Review
Clinical Review Report

August 2016

Drug	Ticagrelor (Brilinta)
Indication	Co-administered with low-dose acetylsalicylic acid (ASA: 75-150 mg), is indicated for the secondary prevention of atherothrombotic events in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event.
Listing request	Co-administered with low-dose acetylsalicylic acid (ASA: 75-150 mg), is indicated for the secondary prevention of atherothrombotic events in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event
Dosage form(s)	60 mg tablets
NOC date	May 30, 2016
Manufacturer	AstraZeneca Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

ADP	adenosine diphosphate
AE	adverse event
ASA	acetylsalicylic acid
CABG	coronary artery bypass graft
CDEC	CADTH Canadian Drug Expert Committee
CI	confidence interval
CV	cardiovascular
DB	double-blind
EQ-5D	EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial
HR	hazard ratio
HRQoL	health-related quality of life
HSF	Heart and Stroke Foundation
ISTH	International Society on Thrombosis and Haemostasis
KM%	Kaplan–Meier percentage at 36 months
MCID	minimal clinically important difference
MI	myocardial infarction
NNH	number needed to harm
PCI	percutaneous coronary intervention
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
TIMI	Thrombolysis in Myocardial Infarction
VAS	visual analogue scale

EXECUTIVE SUMMARY

Introduction

Myocardial infarction (MI) is usually caused by blockage of a coronary artery that results in myocardial tissue death.[1] In 2014 to 2015, there were 69,762 in-patient hospitalizations for acute MI in Canada,[2] and although mortality rates have been declining, MI is associated with significant morbidity and mortality.[3] Patients report having to take medication multiple times a day, frequent visits to a health care provider, taking time off work, and limitations to their activities following their MI.

Ticagrelor is an oral, direct-acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated $P2Y_{12}$-dependent platelet activation and aggregation.[4] The new indication is ticagrelor, combined with low-dose (75 mg to 150 mg) acetylsalicylic acid (ASA), for the secondary prevention of atherothrombotic events in adult patients with a history of MI (occurred at least one year ago) and a high risk of developing an atherothrombotic event. The recommended dose is 60 mg twice daily, orally. Health Canada has specified that treatment can be initiated up to two years from the spontaneous MI, or within one year after stopping previous ADP receptor antagonist treatment, and that treatment duration is not to exceed three years of extended treatment.

Ticagrelor is also approved for the secondary prevention of atherothrombotic events (in combination with ASA) in patients with acute coronary syndromes (unstable angina, non–ST elevation MI, or ST elevation MI) who are to be managed medically and those who are to be managed with percutaneous coronary intervention (PCI) (with or without stent) and/or coronary artery bypass graft (CABG). The CADTH Canadian Drug Expert Committee (CDEC) recommended that ticagrelor not be listed for this indication at the submitted price.[5]

Indication under review
Co-administered with low-dose ASA (75-150 mg), for the secondary prevention of atherothrombotic events in patients with a history of MI (occurred at least one year ago) and a high risk of developing an atherothrombotic event
Listing criteria requested by sponsor
Co-administered with low-dose (75-150 mg) acetylsalicylic acid (ASA), for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event.

The objective was to perform a systematic review of the beneficial and harmful effects of ticagrelor 60 mg and 90 mg tablets co-administered with low-dose (75 mg to 150 mg) ASA, for the prevention of atherothrombotic events in adult patients with a history of MI that occurred at least one year ago, and a high risk of developing an atherothrombotic event.

Results and interpretation

Included studies

One double-blind (DB) randomized controlled trial (RCT) (PEGASUS) tested the superiority of ticagrelor 90 mg or 60 mg twice daily versus placebo (as add-on therapy to low-dose ASA) in patients older than 50 years with a history of MI (one year to three years before randomization), and with one of the following

risk factors for atherothrombotic events: age ≥ 65 years; diabetes requiring medication; second prior spontaneous MI (> 1 year ago); angiographic evidence of multi-vessel coronary artery disease; or chronic renal dysfunction (creatinine clearance < 60 mL/min). The patients enrolled in the PEGASUS study (N = 21,162) had a mean age of 65 years and were predominantly Caucasian (87%) and male (76%).

The primary outcome was time to first occurrence of cardiovascular (CV) death, MI, or stroke. Other outcomes included time to CV mortality, all-cause mortality, stent thrombosis, or bleeding events. PEGASUS was an event-driven trial and patients were followed for a minimum of 12 months and until at least 1,360 primary efficacy events had occurred (median follow-up 33 months). Primary efficacy events and bleeding events were adjudicated by an independent committee.

This review focused on the comparison between placebo and ticagrelor 60 mg twice daily, as this was the dose requested by the manufacturer for Health Canada approval.

Efficacy

In the PEGASUS study at 36 months, the Kaplan–Meier percentage (KM%) of patients who experienced a primary composite event (CV death, MI, or stroke) was 7.8% in the ticagrelor 60 mg twice daily plus low-dose ASA group compared with 9.0% in the low-dose ASA plus placebo group, and was statistically significant (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.74 to 0.95). No significant differences were detected between groups in time to CV mortality or all-cause mortality. The frequency of MI (4.5 KM% versus 5.2 KM%) and stroke (1.5 KM% versus 1.9 KM%) were lower in the ticagrelor 60 mg versus placebo groups. The incidence of stent thrombosis was [redacted] and [redacted] for ticagrelor versus placebo in the subgroup of patients with a coronary stent at baseline ([redacted]).

[redacted]

Subgroup analyses based on region, history of more than one MI, multi-vessel coronary artery disease, prior PCI, coronary stent implantation, or diabetes showed similar results to the overall population for the primary composite outcome. Subgroup analyses based on the time from qualifying MI or time from prior ADP therapy suggest that patients who remained stable on ASA alone (i.e., patients with MI more than two years prior or who had stopped ADP therapy more than 12 months prior to enrolment) may not benefit from re-initiation of dual antiplatelet therapy. Although the interaction terms for these analyses did not reach statistical significance, the product monograph does not recommend re-initiating dual antiplatelet therapy if more than two years have passed since the patient's spontaneous MI, or more than one year after stopping previous ADP receptor antagonist treatment.[4]

Harms

Most patients in the PEGASUS study (69% to 76%) reported one or more adverse events (AEs), including bleeding events (29% versus 12%) and dyspnea (14% versus 6%), which were reported more frequently among patients who received ticagrelor 60 mg than placebo. More patients stopped treatment due to AEs in the ticagrelor 60 mg group than the placebo group (16% versus 9%); however, the frequency of serious adverse events (SAEs) was the same in the treatment groups (22%).

The most notable AE was the increased risk of bleeding with ticagrelor versus placebo. Ticagrelor 60 mg twice daily was associated with an increased risk of adjudicated bleeding events based on Thrombolysis

in Myocardial Infarction (TIMI), PLATO (AstraZeneca study D5130C5262, "A Study of PLATelet Inhibition and Patient Outcomes"), GUSTO (the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial), and International Society on Thrombosis and Haemostasis (ISTH) criteria (HR range 2.3 to [redacted]). The absolute risk of bleeding, however, depended on the definition used and ranged from 2.3 KM% (TIMI major bleeding) to [redacted](ISTH major or minor clinically relevant bleeding) in the ticagrelor 60 mg group. Based on the absolute risk difference of TIMI major bleeding, the number needed to harm (NNH) was 81 patients. The risk of bleeding appeared to be constant over time, and subgroup analyses showed that the risk of bleeding was generally consistent across different patient groups. The risk of intracranial hemorrhage or fatal bleeding was low, and numerically more patients in the ticagrelor 60 mg group experienced an intracranial hemorrhage compared with placebo. However, we are unable to draw any conclusions with regard to intracranial hemorrhage or fatal bleeding given that the study was not powered to test for differences between treatments.

The analysis of time to first occurrence of CV mortality, MI, stroke, or TIMI major bleeding did not show a difference between groups (HR, 0.95; 95% CI, 0.85 to 1.06). The clinical importance of the observed absolute risk reduction in major CV events (risk difference [RD] –1.3%; 95% CI, –2.3% to –0.3%) should be interpreted in the context of the increased risk of major bleeding ([redacted]).

Conclusions

Ticagrelor 60 mg twice daily plus ASA appears to have contributed to a reduced risk in CV death, MI, or stroke over a three-year period, compared with ASA alone, among patients with a history of MI and additional atherothrombotic risk factors. No clinically important differences were observed in terms of CV mortality, all-cause mortality, or [redacted]with ticagrelor 60 mg plus ASA over ASA alone, based on data from a single RCT. No conclusions can be made with regard to the impact of ticagrelor on stent thrombosis, fatal bleeding, or non-fatal intracranial hemorrhage, due to the low incidence of events.

Ticagrelor 60 mg plus ASA was associated with an increased frequency of dyspnea, and clinically important major bleeding events, versus ASA alone. The net clinical benefit did not show a clear advantage for ticagrelor plus ASA versus ASA alone based on the analysis of time to CV mortality, MI, stroke, or TIMI major bleeding. The clinical importance of the reduction in major CV events needs to be evaluated, however, relative to the observed increased risk of major bleeding.

As the median treatment duration in the trial was 29 months, the risks and benefits for longer-term treatment durations are uncertain.

TABLE 1: SUMMARY OF RESULTS

Outcome	PEGASUS		
Time to First Event	**Placebo N = 7,067**	**Ticagrelor 60 mg N = 7,045**	**Ticagrelor 90 mg N = 7,050**
All-Cause Mortality			
n (%)	326 (4.6)	289 (4.1)	326 (4.6)
Kaplan–Meier % at 36 months	5.2	4.7	5.1
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		0.89 (0.76 to 1.04)	1.00 (0.86 to 1.16)
P value		NS[a]	NS[a]
CV Mortality			
n (%)	210 (3.0)	174 (2.5)	182 (2.6)
Kaplan–Meier % at 36 months	3.4	2.9	2.9
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		0.83 (0.68 to 1.01)	0.87 (0.71 to 1.06)
P value		0.068	0.15
CV Mortality, MI, or Stroke			
n (%)	578 (8.2)	487 (6.9)	493 (7.0)
Kaplan–Meier % at 36 months	9.0	7.8	7.8
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		0.84 (0.74 to 0.95)	0.85 (0.75 to 0.96)
P value		0.0043	0.0080
NNT (36 months)		79	[redacted]
MI			
n (%)	338 (4.8)	285 (4.0)	275 (3.9)
Kaplan–Meier % at 36 months	5.2	4.5	4.4
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		0.84 (0.72 to 0.98)	0.81 (0.69 to 0.95)
P value		0.031[b]	0.010[b]
Stroke			
n (%)	122 (1.7)	91 (1.3)	100 (1.4)
RD (95% CI) versus placebo		[redacted]	[redacted]
Kaplan–Meier % at 36 months	1.9	1.5	1.6
HR (95% CI) versus placebo		0.75 (0.57 to 0.98)	0.82 (0.63 to 1.07)
P value		0.034[b]	0.14[b]
SAE			
n (%)	1,511 (22)	1,499 (22)	1,514 (22)
WDAE			
n (%)	596 (9)	1,117 (16)	1,306 (19)
Notable Harms			
Any dyspnea event, n (%)	382 (5)	986 (14)	1,204 (17)
TIMI Major bleeding	N = 6,996	N = 6,958	N = 6,988
n (%)	54 (0.8)	115 (1.7)	127 (1.8)
Kaplan–Meier % at 36 months	1.1	2.3	2.6

Outcome	PEGASUS		
Time to First Event	**Placebo N = 7,067**	**Ticagrelor 60 mg N = 7,045**	**Ticagrelor 90 mg N = 7,050**
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		2.32 (1.68 to 3.21)	2.69 (1.96 to 3.70)
P value		< 0.0001[b]	< 0.0001[b]
NNH (36 months)		81	65
TIMI Major or Minor Bleeding			
n (%)	72 (1.0)	168 (2.4)	192 (2.7)
Kaplan–Meier % at 36 months	1.4	3.4	3.9
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		2.54 (1.93 to 3.35)	3.05 (2.32 to 4.00)
P value		< 0.0001[b]	< 0.0001[b]
NNH (36 months)		[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; RD = risk difference; SAE = serious adverse event; TIMI = Thrombolysis in Myocardial Infarction; WDAE = withdrawal due to adverse event.

[a] Not statistically significant due to non-significant results in prior outcome (i.e., CV mortality) in the statistical testing procedure.

[b] Exploratory outcome.

[c] Calculated by CADTH.

Source: Clinical Study Report,[6] CADTH Common Drug Review submission,[7] additional data supplied by manufacturer.[8]

1. INTRODUCTION

1.1 Disease prevalence and incidence

Myocardial infarction (MI) is usually caused by blockage of a coronary artery that results in myocardial tissue death.[1] The rupture or fissuring of an unstable atherosclerotic plaque is often the precipitating factor that leads to platelet activation and aggregation, and subsequent thrombus formation.[9]

In 2014 to 2015, there were 69,762 in-patient hospitalizations for acute MI in Canada.[2] Although mortality rates have been declining, MI is associated with significant morbidity and mortality.[3] Patients report having to take medication multiple times a day, frequent visits to a health care provider, taking time off work, and limitations to their activities following their MI.

1.2 Standards of therapy

Patients with MI have heightened platelet activation and aggregation and are at increased risk of recurrent ischemic events.[9] Canadian and US guidelines recommend dual antiplatelet therapy, with ASA plus either clopidogrel, ticagrelor, or prasugrel, for up to the first 12 months following an acute MI.[1,3,10,11] After the first year, ASA is the standard of care for the long-term secondary prevention of atherothrombotic events. Clopidogrel monotherapy is also indicated for long-term secondary prevention in patients with prior MI and may be used in place of acetylsalicylic acid (ASA) in some patients (Table 2).[11,12]

1.3 Drug

Ticagrelor is an oral, direct-acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated $P2Y_{12}$-dependent platelet activation and aggregation.[4] The new indication for ticagrelor is as follows: co-administered with low-dose (75 mg to 150 mg) acetylsalicylic acid (ASA), for the prevention of atherothrombotic events in adult patients with a history of MI (occurred at least one year ago) and a high risk of developing an atherothrombotic event. The recommended dose is 60 mg twice daily, orally. Health Canada has specified that no loading dose is required, and the 90 mg dose should not be used for this indication. Health Canada has also specified that treatment can be initiated up to two years from the spontaneous myocardial infarction, or within one year after stopping previous ADP receptor antagonist treatment, and that treatment duration is not to exceed three years of extended treatment.

Ticagrelor is also approved for the secondary prevention of atherothrombotic events (in combination with ASA) in patients with acute coronary syndromes (unstable angina, non–ST elevation MI, or ST elevation MI) who are to be managed medically and those who are to be managed with percutaneous coronary intervention (PCI) (with or without stent) and/or coronary artery bypass graft (CABG). The CADTH Canadian Drug Expert Committee (CDEC) recommended that ticagrelor not be listed at the submitted price for the following reasons:

- The pre-specified subgroup analysis (by region), in the one large randomized controlled trial (RCT) of patients with acute coronary syndrome, did not provide evidence of the superiority of ticagrelor compared with clopidogrel in a North American patient population to support a higher price for ticagrelor.
- Given the limitations identified with the manufacturer's pharmacoeconomic submission, CDEC noted that the cost-effectiveness of ticagrelor could not be properly assessed.
- The daily cost of ticagrelor ($2.96) is greater than clopidogrel ($2.58).[5]

Indication under review
Co-administered with low-dose ASA (75-150 mg), for the secondary prevention of atherothrombotic events in patients with a history of MI (occurred at least one year ago) and a high risk of developing an atherothrombotic event
Listing criteria requested by sponsor
Co-administered with low-dose (75-150 mg) ASA, for the prevention of atherothrombotic events in adult patients with a history of MI (occurred at least one year ago) and a high risk of developing an atherothrombotic event

TABLE 2: KEY CHARACTERISTICS OF PLATELET AGGREGATION INHIBITORS

	Ticagrelor	Clopidogrel	Prasugrel	ASA
Mechanism of action	$P2Y_{12}$ receptor blocker	$P2Y_{12}$ receptor blocker (prodrug)	$P2Y_{12}$ receptor blocker	Inhibits thromboxane A_2 synthesis
Indication[a]	Co-administered with low-dose ASA for the secondary prevention of atherothrombotic events in patients with a history of MI (occurred at least one year ago) and a high risk of developing an atherothrombotic event	Secondary prevention of atherothrombotic events (MI, stroke, and vascular death) in patients with atherosclerosis documented by stroke, MI, or established peripheral arterial disease		Secondary prevention following MI
	Co-administered with ASA, for the secondary prevention of atherothrombotic events in patients with acute coronary syndromes	In combination with ASA, for the early and long-term secondary prevention of atherothrombotic events in patients with acute coronary syndromes	Co-administered with ASA, for the early and long-term secondary prevention of atherothrombotic events in patients with ACS as follows: – unstable angina or NSTEMI managed with PCI – STEMI managed with primary or delayed PCI	Reduction of platelet aggregation and prevention of clot-related complications (non-fatal MI, non-fatal stroke, and death) in acute STEMI, NSTEMI, and unstable angina
Route of administration	Oral	Oral	Oral	Oral
Recommended dose[b]	60 mg twice daily	75 mg daily	10 mg daily	80 mg to 162 mg daily
Serious side effects/ safety issues	Bleeding, use with caution in patients with bradycardia Contraindications: active bleeding, history of intracranial hemorrhage, severe hepatic impairment, hypersensitivity, taking strong CYP3A4 inhibitors	Bleeding, TTP, acquired hemophilia Contraindications: active bleeding, significant hepatic impairment, hypersensitivity Common: bleeding, rash, dyspepsia, abdominal pain, and	Bleeding (use with caution in those ≥ 75 years old or < 60 kg body weight), TTP Contraindications: active bleeding, history of stroke or TIA, severe hepatic impairment, hypersensitivity	Use caution in patients with decreased renal function, bleeding tendencies, significant anemia, hypoprothrombinemia, thrombocytopenia, vitamin K deficiency or severe hepatic disease

	Ticagrelor	Clopidogrel	Prasugrel	ASA
	Common: bleeding, dyspnea, headache	diarrhea	Common: bleeding, rash, anemia	Contraindications: active peptic ulcer, hypersensitivity Common: gastrointestinal toxicity

ACS = acute coronary syndrome; ASA = acetylsalicylic acid; MI = myocardial infarction; NSTEMI = non–ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST segment elevation myocardial infarction; TIA = transient ischemic attack; TTP = thrombotic thrombocytopenic purpura.
[a] Health Canada indication.
[b] Recommended dose for long-term secondary prevention.
Source: Product monographs.[4,12-14]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ticagrelor 60 mg and 90 mg tablets co-administered with low-dose (75 mg to 150 mg) ASA, for the prevention of atherothrombotic events in adult patients with a history of MI that occurred at least one year ago, and a high risk of developing an atherothrombotic event.

Note: this review was initiated prior to ticagrelor receiving a Notice of Compliance (NOC) for patients with a history of MI that occurred at least one year ago. Thus, both doses of ticagrelor were included in the report as the final recommended dosage was not known.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with a history of MI that occurred at least one year ago, and a high risk of developing an atherothrombotic event **Subgroups:** – Region – Prior PCI or bypass surgery (yes/no) – Prior stent (yes/no) – Recurrent MI (> 1 MI/1 MI) – Multi-vessel CAD disease (yes/no) – Diabetes (yes/no).
Intervention	Ticagrelor 60 mg or 90 mg twice daily in combination with low-dose ASA (75 mg to 150 mg daily)
Comparators	– Clopidogrel – ASA
Outcomes	**Key efficacy outcomes:** **Efficacy:** – Mortality (all causes, CV related) – MI – Stroke – Stent thrombosis – HRQoL. **Other efficacy outcomes:** – Health care resource utilization. **Harms outcomes:** AEs, SAEs, WDAEs, bleeding events, dyspnea, bradyarrhythmia
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; ASA = acetylsalicylic acid; CAD = coronary artery disease; CV = cardiovascular; HRQoL = health-related quality of life; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse events.

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Brilinta (ticagrelor).

Methodological filters were applied to limit retrieval to RCTs and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See 0 for the detailed search strategies.

The initial search was completed on March 18, 2016. Regular alerts were established to update the search until the meeting of CDEC on July 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3.

3. RESULTS

3.1 Findings from the literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

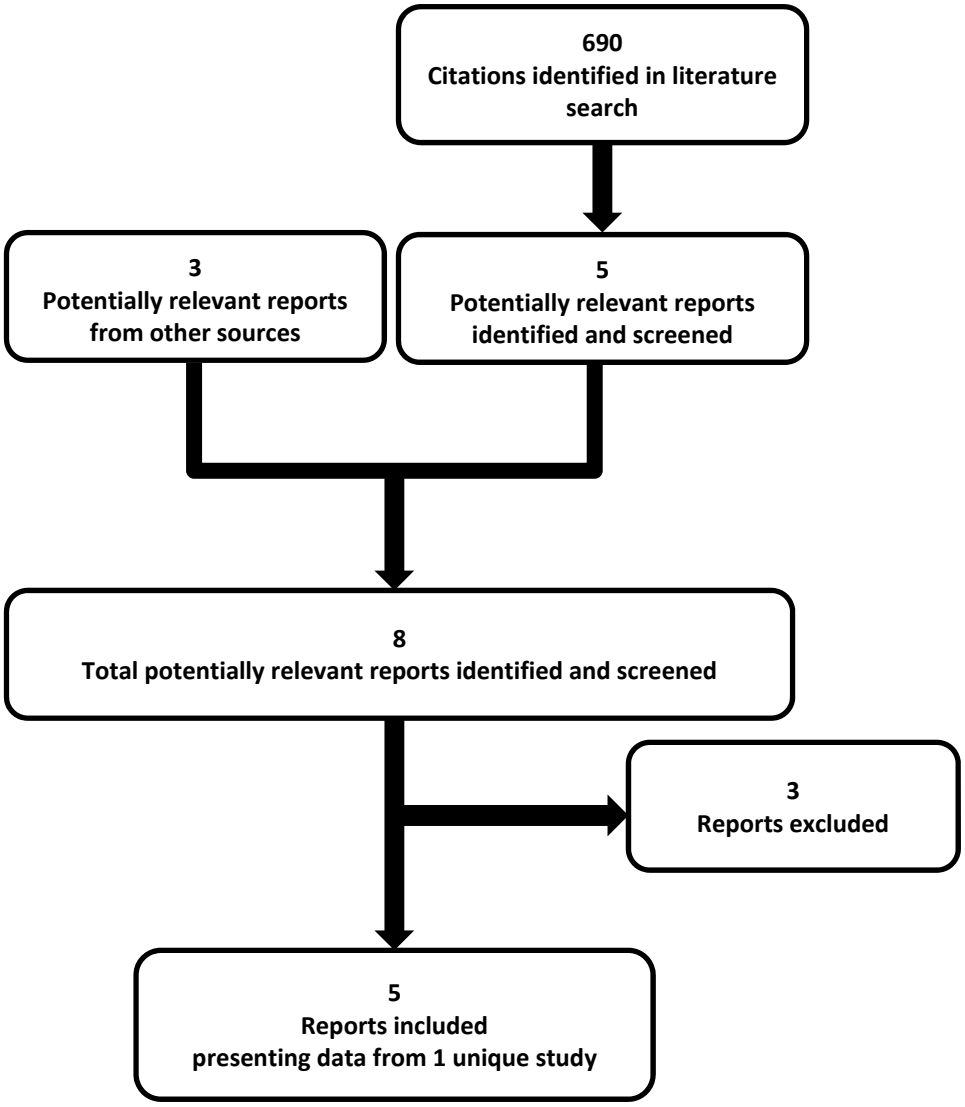


TABLE 4: DETAILS OF INCLUDED STUDIES

		PEGASUS
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	Europe, Canada, US, Asia, South America, South Africa
	Randomized (N)	21,162
	Inclusion Criteria	• Adults > 50 years of age • Spontaneous MI 1 year to 3 years prior • One of the following risk factors: age ≥ 65 years; diabetes requiring medication; second prior spontaneous MI; multi-vessel coronary artery disease; or chronic renal dysfunction (CrCl < 60 mL/min) • Currently prescribed and tolerating ASA; able to continue on 75 mg to 150 mg daily for study duration
	Exclusion Criteria	• Bleeding disorder or gastrointestinal bleeding in past 6 months • Major surgery in past 30 days • History of ischemic stroke or intracranial bleeding • CNS tumour or intracranial vascular abnormality • Planned use of $P2Y_{12}$ receptor antagonist, dipyridamole, cilostazol, or anticoagulant therapy • Planned coronary, cerebrovascular, or peripheral arterial revascularization • CABG in past 5 years • At risk of bradycardic events • Renal failure requiring dialysis or anticipated need for dialysis
DRUGS	**Intervention**	Ticagrelor 90 mg twice daily, or ticagrelor 60 mg twice daily, in combination with ASA 75 mg to 150 mg daily
	Comparator(s)	Placebo, in combination with ASA 75 mg to 150 mg daily
DURATION	**Phase**	3
	DB	Event-driven trial (target 1,360 primary events) and 12 months' minimum follow-up period
	Safety follow-up	2 to 4 weeks
OUTCOMES	**Primary End Point**	Time to first occurrence of CV death, MI, or stroke
	Other End Points	• CV mortality • All-cause mortality • MI • Stroke • Stent thrombosis • EQ-5D • TIMI major bleeding events • Harms
NOTES	**Publications**	Bonaca 2015[15,16]

ASA = acetylsalicylic acid; CABG = coronary artery bypass graft; CrCl = creatinine clearance; CV = cardiovascular; CNS = central nervous system; DB = double-blind; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; MI = myocardial infarction; RCT = randomized controlled trial; TIMI = Thrombolysis in Myocardial Infarction.
Note: Two additional reports were included (Food and Drug Administration [FDA] report,[17] CADTH Common Drug Review submission[7]).
Source: Clinical Study Report.[6]

3.2 Included studies

3.2.1 Description of studies

One double-blind (DB) RCT (PEGASUS-TIMI 54) met the inclusion criteria. PEGASUS tested the superiority of ticagrelor 90 mg and 60 mg twice daily versus placebo (as add-on therapy to low-dose ASA) in patients older than 50 years with a history of MI (one year to three years prior to randomization), and who were at high risk of atherothrombotic events.

Patients were randomized 1:1:1 (stratified by site) to ticagrelor 90 mg twice daily, 60 mg twice daily, or placebo, using a central interactive voice or Web response system. PEGASUS was an event-driven trial and patients were followed for a minimum of 12 months and until at least 1,360 primary efficacy events occurred (cardiovascular [CV] death, MI, or stroke). The median follow-up was 33.1, 33.3, and 33.1 months, in the placebo, ticagrelor 60 mg, and ticagrelor 90 mg groups, respectively.

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients older than 50 years who had a spontaneous MI one year to three years prior and were currently taking ASA were eligible for enrolment. In addition, patients had one of the following risk factors:

- age ≥ 65 years
- diabetes requiring medication
- second prior spontaneous MI (more than one year ago)
- angiographic evidence of multi-vessel coronary artery disease
- chronic renal dysfunction (creatinine clearance < 60 mL/min).

Patients were not required to have previously taken an ADP receptor blocker prior to enrolment.

The exclusion criteria included patients with a higher risk of bleeding (e.g., those with a bleeding diathesis or coagulation disorder, gastrointestinal bleeding in the past six months, major surgery in the past 30 days, history of ischemic stroke or intracranial hemorrhage, or those who require anticoagulation) or bradycardia (e.g., sick sinus syndrome, second- or third-degree heart block unless treated with a pacemaker). The enrolment criteria were changed in a protocol amendment, four months after the start of the trial, which excluded those with history of ischemic stroke, central nervous system tumour, or intracranial vascular abnormality, or intracranial or spinal cord surgery within the last five years. Those with stroke were excluded due to publication of studies with other ADP inhibitors suggesting that more intensive antiplatelet therapy might pose high risk of intracranial hemorrhage in patients with a history of ischemic stroke. The manufacturer stated that the other conditions were excluded because these they are associated with an increased risk of intracranial or intraspinal hemorrhage. These changes affected 102 patients who no longer met the inclusion criteria, and had their study drug stopped but were followed for the remainder of the study.

b) Baseline characteristics

The patients enrolled in the PEGASUS study had a mean age of 65 years and were predominantly Caucasian (87%) men (76%) (Table 5). The baseline characteristics were balanced between treatment groups. Key medications used at baseline are summarized in Table 6. In the week prior to randomization, 26% of patients in each treatment group were receiving dual therapy with ASA and an ADP receptor blocker. Among these patients, clopidogrel was the most commonly used ADP blocker

(24% of those enrolled). [redacted] (Table 7). Very few patients (< 1%) were enrolled who reported bleeding or other adverse events (AEs) as the reason for stopping ADP receptor blockers.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	Placebo N = 7,067	Ticagrelor 60 mg N = 7,045	Ticagrelor 90 mg N = 7,050
Age — years, mean (SD)	65.4 (8.3)	65.2 (8.4)	65.4 (8.4)
Age > 75 years, n (%)	[redacted]	[redacted]	[redacted]
Caucasian, n (%)	6,124 (87)	6,077 (86)	6,126 (87)
Male, n (%)	5,350 (76)	5,384 (76)	5,368 (76)
Weight (kg), mean (SD)	81.8 (16.6)	82.0 (17.0)	82.0 (16.7)
BMI ≥ 30, n (%)	[redacted]	[redacted]	[redacted]
Current smoker	1,143 (16)	1,206 (17)	1,187 (17)
Former smoker	[redacted]	[redacted]	[redacted]
Time from qualifying MI to randomization (months), mean (SD)[a]	[redacted]	[redacted]	[redacted]
Type of MI			
STEMI	3,809 (54)	3,757 (53)	3,763 (53)
NSTEMI	2,843 (40)	2,842 (40)	2,898 (41)
History of PCI	5,835 (83)	5,874 (83)	5,846 (83)
Received a stent	[redacted]	[redacted]	[redacted]
Bare metal stent	[redacted]	[redacted]	[redacted]
Drug eluting stent	[redacted]	[redacted]	[redacted]
Hypertension requiring medication	5,484 (78)	5,461 (78)	5,462 (78)
Hypercholesterolemia requiring medication	5,451 (77)	5,380 (76)	5,410 (77)
Atherothrombotic risk factors			
Age ≥ 65 years	3,907 (55)	3,755 (53)	3,855 (55)
Diabetes requiring medication	1,999 (28)	2,022 (29)	2,006 (29)
History of > 1 MI	1,188 (17)	1,168 (17)	1,143 (16)
Multi-vessel coronary artery disease	4,213 (60)	4,190 (60)	4,155 (59)
Chronic renal dysfunction	423 (6)	403 (6)	428 (6)

BMI = body mass index; MI = myocardial infarction; NSTEMI = non–ST elevated myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; STEMI = ST elevated myocardial infarction.

[a] A total of 291 patients (1.4%) had their qualifying MI outside of the prior one- to three-year period specified in the protocol (< 1 year, n = 141; > 3 years, N = 117), information on qualifying MI was not known (n = 7), or the patient did not have a prior MI (n = 26); however, the distribution of these patients was similar across treatment groups.

Source: Clinical Study Report.[6]

TABLE 6: MEDICATIONS TAKEN AT BASELINE

Drug Class	Placebo N = 7,067	Ticagrelor 60 mg N = 7,045	Ticagrelor 90 mg N = 7,050
ASA	[redacted]	[redacted]	[redacted]
ADP receptor blocker	[redacted]	[redacted]	[redacted]
Clopidogrel	[redacted]	[redacted]	[redacted]
Prasugrel	[redacted]	[redacted]	[redacted]
Ticagrelor	[redacted]	[redacted]	[redacted]
Ticlopidine	[redacted]	[redacted]	[redacted]
Beta blocker	[redacted]	[redacted]	[redacted]
Lipid-lowering drug	[redacted]	[redacted]	[redacted]
ACEI	[redacted]	[redacted]	[redacted]
ARB	[redacted]	[redacted]	[redacted]
CCB	[redacted]	[redacted]	[redacted]
Nitrates	[redacted]	[redacted]	[redacted]
Antiarrhythmics	[redacted]	[redacted]	[redacted]
Proton pump inhibitor	[redacted]	[redacted]	[redacted]

ACEI = angiotensin-converting enzyme inhibitor; ADP = adenosine diphosphate; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; CCB = calcium channel blockers.
Note: Includes medications taken within 7 days prior to or at randomization.
Source: Clinical Study Report.[6]

TABLE 7: PREVIOUS TREATMENT WITH ADENOSINE DIPHOSPHATE RECEPTOR BLOCKER (ANY TIME PRIOR TO RANDOMIZATION)

Drug	Placebo N = 7,067	Ticagrelor 60 mg N = 7,045	Ticagrelor 90 mg N = 7,050
Prior ADP receptor blocker	6,285 (89)	6,289 (89)	6,271 (89)
Clopidogrel	5,878 (83)	5,915 (84)	5,922 (84)
Prasugrel	325 (5)	317 (5)	287 (4)
Ticagrelor	38 (< 1)	26 (< 1)	31 (< 1)
Ticlopidine	38 (< 1)	35 (< 1)	34 (< 1)
Time from last dose to randomization			
0 to 7 days	1,828 (26)	1,816 (26)	1,826 (26)
8 to 90 days	1,243 (18)	1,257 (18)	1,243 (18)
3 to 12 months	1,540 (22)	1,520 (22)	1,498 (21)
> 12 months	1,645 (23)	1,661 (24)	1,676 (24)
Reason treatment stopped			
Physician recommendation	[redacted]	[redacted]	[redacted]
Patient preference	[redacted]	[redacted]	[redacted]
Bleeding	9 (< 1)	9 (< 1)	9 (< 1)
Other adverse event	[redacted]	[redacted]	[redacted]

ADP = adenosine diphosphate.
Source: Clinical Study Report.[6]

3.2.3 Interventions

In the PEGASUS study, patients received ticagrelor 60 mg, ticagrelor 90 mg, or placebo twice daily, and a double-dummy design was used to maintain blinding. All but nine patients continued on ASA during the trial, and > 99% received the per-protocol dose of 75 mg to 150 mg daily.

For any patient who developed an indication for an ADP receptor blocker (i.e., acute coronary syndrome or percutaneous intervention), selection of the drug was determined by the local investigator. If clopidogrel was selected as the ADP blocker, it was recommended that patients receive the new blinded study drug via the interactive voice or Web response system to replace their existing study drug. Patients previously randomized to ticagrelor 60 mg or 90 mg dosage groups were given ticagrelor 90 mg plus clopidogrel placebo, and those randomized to placebo received clopidogrel loading and then maintenance doses (75 mg daily) plus ticagrelor placebo. All patients continued on ASA. Loading doses of ADP receptor blockers could be administered if indicated, and patients with an urgent need for ADP receptor blockade could receive open-label (OL) ADP antagonists and temporarily stop the study drug. In the PEGASUS trial, [redacted], [redacted], and [redacted] of patients in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively, received modified study treatment for ADP receptor blockade. OL prasugrel could be given as an alternative, and the study drug was stopped for the duration of the prasugrel treatment. No rationale was provided for selecting clopidogrel over prasugrel as the blinded control ADP inhibitor.

Due to potential drug interactions, concurrent use of simvastatin or lovastatin (at doses > 40 mg/day), or drugs that inhibit the cytochrome P-450 isoenzyme (CYP) 3A, was not allowed. Other prohibited medications included oral or parenteral anticoagulants, and caution was advised with concurrent use of nonsteroidal anti-inflammatory drugs, fibrinolytics, and CYP3A inducers. The use of glycoprotein IIb/IIIa antagonists was allowed. Investigators were advised to stop the study drug five days before elective major surgery.

Although non-study use of antithrombotic drugs was not allowed during the trial, [redacted] of patients received clopidogrel, [redacted] received ticagrelor, [redacted] used heparin-like drugs and [redacted] used vitamin K antagonists at one point during the trial (either on or off study drug treatment). Of note: these percentages do not include the [redacted] to [redacted] who received modified study treatment with ADP receptor blockers, as mentioned above. The proportion of patients using non-study antithrombotic drugs and other medications was generally similar between treatment groups.

3.2.4 Outcomes

The primary outcome was time to first occurrence of CV death, MI, or stroke. Secondary outcomes included:

- Time to CV mortality
- Time to all-cause mortality.

Other outcomes of interest were reported as exploratory analyses, including:

- Time to MI
- Time to stroke
- Time to CV mortality, stroke, MI, or Thrombolysis in Myocardial Infarction (TIMI) major bleeding
- Time to stent thrombosis
- EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) visual analogue scale (VAS) and index scores

- Time to bleeding event defined using TIMI, PLATO (AstraZeneca study D5130C5262, "A Study of PLATelet Inhibition and Patient Outcomes"), GUSTO (the "Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries" trial), and International Society on Thrombosis and Haemostasis (ISTH) criteria.

Potential efficacy or bleeding events were adjudicated by a blinded independent end point committee. Efficacy events reviewed included deaths, cardiac ischemic events (MI, urgent coronary revascularization, unstable angina) and cerebrovascular events (stroke or transient ischemic attack [TIA]). Definitions of the efficacy events were provided in the protocol and those used for the primary composite outcome have been presented in Appendix 4, Table 20. Minimal bleeding events were those with no involvement of a critical area, no clinical signs, and no medical examination or intervention. Non-minimal bleeding events were adjudicated using the TIMI, PLATO, GUSTO, and ISTH definitions (Table 8; Appendix 4, Table 21). Any deaths that occurred after withdrawal of consent were adjudicated based on publicly available data sources and included in the all-cause mortality analysis. Patients were evaluated every four months for the first year, then every six months, and at the end of treatment.

Health-related quality of life (HRQoL) was measured using the EQ-5D, a generic, non–disease-specific measure of health status.[11] The tool is based on self-report of five domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. The index score is calculated by applying a country-specific, utility function–based scoring algorithm to the EQ-5D health states and an index score of 1 represents the best possible health and 0 represents death, with the possibility of health states being valued as worse than death (< 0). The EQ-5D is also accompanied by a VAS to provide a self-rating of overall health, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[11] A minimal clinically important difference (MCID) for EQ-5D index or VAS scores in post-MI patients was not identified in the literature, but in general use, the MCID for the index score ranges from 0.033 to 0.074.[13]

AEs were defined as the development of undesirable medical conditions or the deterioration of a pre-existing medical conditions following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. Serious adverse events (SAEs) were any AEs that were life-threatening or resulted in death, required hospitalization, or resulted in persistent disability. Non-fatal efficacy events (e.g., MI) were not included as AEs, except for intracranial hemorrhage, which was included as both an efficacy and AE. Suspected efficacy events that were assessed by the adjudication committee and rated as not meeting the efficacy event criteria (e.g., "not a stroke"), were tabulated separately, even those that met the criteria for an AE of interest. Events that occurred from the first dose of treatment until seven days after the last dose were included in the safety analysis (on-treatment analysis). All deaths were reported as SAEs as well as efficacy end points.

TABLE 8: THROMBOLYSIS IN MYOCARDIAL INFARCTION DEFINITION OF BLEEDING EVENTS

Major Bleeding	Minor Bleeding	Bleeding Requiring Medical Attention	Minimal Bleeding
Intracranial bleeding, or Clinically overt signs of hemorrhage associated with a drop in Hgb ≥ 50 g/L (or hematocrit ≥ 15%), or Fatal bleeding	Clinically overt sign of hemorrhage associated with a fall in Hgb of 3 g/L to ≤ 50 g/L (or fall in hematocrit of 9% to < 15%)	Any overt sign of hemorrhage that meets one of the following criteria and that does not meet criteria for a major or minor bleeding event: – Requiring intervention: medical practitioner-guided medical or surgical treatment to stop or treat bleeding including temporarily or permanently discontinuing or changing the dose of a medication or study drug; or – Leading to or prolonging hospitalization; or – Prompting evaluation: leading to unscheduled contact with a health care professional and diagnostic testing (laboratory or imaging).	Any overt bleeding event that does not meet the other criteria

Hgb = hemoglobin.
Source: Clinical Study Report.[6]

3.2.5 Statistical analysis

The primary outcome was time to first occurrence of CV death, MI, or stroke. Ticagrelor 60 mg and ticagrelor 90 mg were analyzed separately versus placebo using a Cox proportional hazards model with a factor for treatment group (*P* values and 95% confidence intervals [CIs] based on the Wald statistic). Kaplan–Meier estimates of the cumulative percentage of patients with a first occurrence of an event were calculated up to 36 months of follow-up. Patients with no events were censored at the study end date, or for those with incomplete follow-up, at the date of withdrawal of consent or last clinical event assessment. In the analysis of CV death, death from other causes was a censoring event. For the analysis of end points not including death, then death was a censoring event. The all-cause mortality analysis included data on deaths from publicly available sources, and event-free patients were censored at the study end date, or at the last date confirmed alive (for those with incomplete follow-up). For the time to bleeding event analyses, patients with no events were censored at the earliest of the following: seven days after the last dose of study drug, death, last contact, or withdrawal of consent.

The Dunnett test was used to control the type I error for the two dose-placebo comparison. One interim analysis was performed when 46% of the expected primary composite events had occurred and the Haybittle–Peto alpha-spending approach was applied to control the type I error; thus the two-sided significance level for each dose-placebo comparison was 0.02598 for the final analysis of the primary outcome. A stepwise hierarchical approach was taken to control for multiplicity for the secondary outcomes (CV mortality and all-cause mortality). If both doses were significant at the previous level, then both doses would be tested, but if only one dose was significant previously, then that dose would be tested on subsequent outcomes. There was no control of multiplicity for other outcomes, including the analysis of time to MI or stroke. Pre-planned subgroup analyses were conducted as exploratory analyses for the following subgroups of interest to this review: region, history of more than one MI, diabetes, prior PCI or coronary stent implantation, or multi-vessel coronary artery disease. Descriptive data were provided for the EQ-5D scores and no statistical testing or imputation of missing data was performed.

The PEGASUS study was an event-driven trial and was to stop when all patients had been followed for a minimum of 12 months and at least 1,360 primary events (CV death, MI, or stroke) had occurred. The study had 89% power for the 90 mg dose and 83% power for the 60 mg dose at a 2.59% significance level (assuming there were two interim analyses) to detect a 20% relative risk reduction with ticagrelor. This was based on an expected 3.5% primary composite event rate per 12 months, a 24-month accrual period and a 14-month follow-up period, and 21,000 patients enrolled.

a) Analysis populations

Efficacy analyses were based on the full analysis set (FAS), which included all patients randomized to treatment. The safety analysis set included all randomized patients who received at least one dose of study drug and had post-dose data (analyzed according to the treatment received).

3.3 Patient disposition

A total of 21,162 patients were randomized to one of three treatment groups in the PEGASUS trial (number screened not reported) (Table 9). Overall, 99.3% of patients remained in the study until the study end date; however, 21% in the placebo group and 29% to 32% of patients in the ticagrelor groups discontinued the study drug prematurely. Most patients (98.7%) had complete follow-up of primary efficacy events.

TABLE 9: PATIENT DISPOSITION

	PEGASUS		
	Placebo	**Ticagrelor 60 mg**	**Ticagrelor 90 mg**
Screened, N	NR		
Enrolled, N	21,326		
Randomized, N (%)	21,162 (99)		
	7,067	7,045	7,050
Did not complete study, N (%)			
Withdrew consent, N (%)	52 (< 1)	50 (< 1)	52 (< 1)
Lost to follow-up, N (%)	1 (< 1)	6 (< 1)	3 (< 1)
Did not receive study drug,[a] N (%)	71 (1)	87 (1)	62 (< 1)
Discontinued study drug,[b] N (%)	1,496 (21)	1,999 (29)	2,233 (32)
Inclusion/exclusion criteria violation that places patient at risk	45 (< 1)	38 (< 1)	32 (< 1)
Adverse events	784 (11)	1,257 (18)	1,434 (21)
Patient decision	590 (8)	635 (9)	689 (10)
Other	61 (< 1)	46 (< 1)	43 (< 1)
Non-compliance with study protocol	16 (< 1)	23 (< 1)	35 (< 1)
FAS, N	7,067	7,045	7,050
Safety, N	6,996	6,958	6,988

FAS = full analysis set; NR = not reported.
[a] Included in FAS but not safety set.
[b] The number of patients who initiated the study drug was used as the denominator to calculate the percentages.
Source: Clinical Study Report.[6]

3.4 Exposure to study treatments

More patients in the ticagrelor 90 mg and ticagrelor 60 mg groups stopped treatment early compared with the placebo group (32% and 29% versus 21%, respectively). The median duration of exposure was

28.3, 29.4, and 30.4 months in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively. In the PEGASUS study, [redacted] of patients were exposed for at least 12 months, and [redacted] were exposed for 24 months in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively.

Approximately one-fourth of patients had one or more temporary discontinuations of study drug (ticagrelor: [redacted], placebo [redacted]). AEs other than bleeding (ticagrelor: [redacted], placebo: [redacted]), invasive procedures (ticagrelor: [redacted], placebo: [redacted]), and bleeding events (ticagrelor [redacted], placebo [redacted]) were the most common reasons for treatment interruption.

3.5 Critical appraisal

3.5.1 Internal validity

The evidence available was limited to one DB RCT (PEGASUS, N = 21,162). Patients were randomized to treatments using accepted methods that included a computer-generated randomization schedule (blocked by study site) and a central interactive voice or Web response system to conceal allocation. The characteristics of patients were similar across treatment groups at baseline. Identical placebo tablets were used to maintain double-blinding, and all efficacy and bleeding events were adjudicated by a blinded, independent end point committee. It is possible that some unblinding may have occurred due to the increased frequency of AEs (bleeding, dyspnea) in patients who received ticagrelor, and this may have affected the reporting of subjective outcomes such as HRQoL.

The efficacy outcomes were assessed using an intention-to-treat (ITT) analysis. Although more patients in the ticagrelor groups stopped treatment early than in the placebo group, these patients continued to be followed until the end of the study unless they withdrew consent (n = 104) or were lost to follow-up (n = 10). Most patients (98.7%) had complete follow-up of primary efficacy events, and vital status information was known for all but 10 patients. The efficacy and bleeding outcomes were analyzed using a Cox proportional hazards model, which takes into consideration the length of follow-up of patients. This method, however, only assessed the time to event for the first occurrence of MI or stroke over the three-year period. The drug effect on subsequent, recurrent events including repeated bleeding was not assessed. Frequent treatment interruptions ([redacted]), early treatment discontinuation (21% versus 29%), and the use of other alternative ADP inhibitors ([redacted]) (placebo versus ticagrelor 60 mg, respectively), even though they reflected real-world practice, could also have biased the estimation of treatment effects. [redacted]. It is unknown how this may have affected the results, considering the small absolute difference between groups for the primary outcome, and given that these events were not included in either the efficacy or AE analyses.

Methods to control type 1 error were employed for the interim analysis, multiple-dose comparison, and the primary and two secondary outcomes. Several other outcomes, including the analysis of two individual components of the primary composite end point (MI or stroke), and the subgroup analyses had no control of multiplicity, and thus statistically significant results should be interpreted with caution. The trial was powered for the primary composite outcome, but not for the individual components of the composite outcome, all-cause mortality, or AEs such as intracranial hemorrhage. The EQ-5D data should be interpreted with caution given that the data were reported for a subset of patients (available case

only), with no imputation for missing data (16% at end-of-treatment visit), and the study was not designed to test for differences in quality of life (QoL).

3.5.2 External validity

According to the expert consulted for this review, the population enrolled in the PEGASUS study varies from the Canadian post-MI population in a number of factors. The patients enrolled were predominately Caucasian males; thus, other races and women may be under-represented. Overall, 12% of the enrolled population were older than 75 years, so data for this age group may be limited. The risk benefit is unknown in patients with certain conditions that were excluded from the PEGASUS trial — namely, patients with a higher risk of bleeding or bradycardia (e.g., sick sinus syndrome, second- or third-degree heart block unless treated with a pacemaker), prior stroke, or intracranial hemorrhage, or who required anticoagulation (e.g., atrial fibrillation, deep venous thrombosis, or pulmonary emboli). In reality, the risk of bleeding could be higher than what was observed in the trial due to the restriction of study population at low risk of bleeding. The trial also excluded patients with a CABG in the past five years. This means that the qualifying MI for all patients was managed either medically or with PCI. No information was provided on the number of patients screened or their characteristics. Overall, 18% of patients were from North America, including 1,306 (6%) Canadians.

The trial applied enrichment criteria with the aim of enrolling a population at high risk of recurrent CV events. The criteria applied, however, were broad and no justification was provided for those criteria selected. According to the clinical expert consulted, the population enrolled was a mixed population that included both higher- and lower-risk patients.

The trial did report outcomes that were clinically relevant and important to patients, including bleeding events, which is one of the key AEs associated with dual antiplatelet therapy. The median ticagrelor exposure duration was 29 months; thus, the risks and benefits for longer-term treatment durations are uncertain.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported in section 2.2, Table 3. (See Table 10 for detailed efficacy data.)

Health Canada has approved the 60 mg dose only for this indication, so this review will focus on the results comparing ticagrelor 60 mg twice daily to placebo. No data were reported on health care resource utilization in the PEGASUS trial.

3.6.1 Mortality

During the PEGASUS trial, 4.6% and 4.1% of patients died in the placebo and ticagrelor 60 mg groups, respectively (Kaplan–Meier percentage at 36 months [KM%]: 5.2% and 4.7%) (Figure 2, Table 10). CV-related deaths were reported in 3.0% (KM%, 3.4) of those who received placebo, and 2.5% (KM%, 2.9) who received ticagrelor 60 mg.

No statistically significant differences were detected between ticagrelor 60 mg and placebo in the time to CV mortality or all-cause mortality (Figure 4). Of note, statistical testing was stopped for all-cause mortality due to the non-significant result in the time to CV mortality, which was the first secondary outcome in the statistical hierarchy.

FIGURE 2: RISK DIFFERENCE FOR KEY OUTCOMES — TICAGRELOR 60 MG VERSUS PLACEBO

[Confidential data regarding risk differences were removed at the manufacturer's request.]

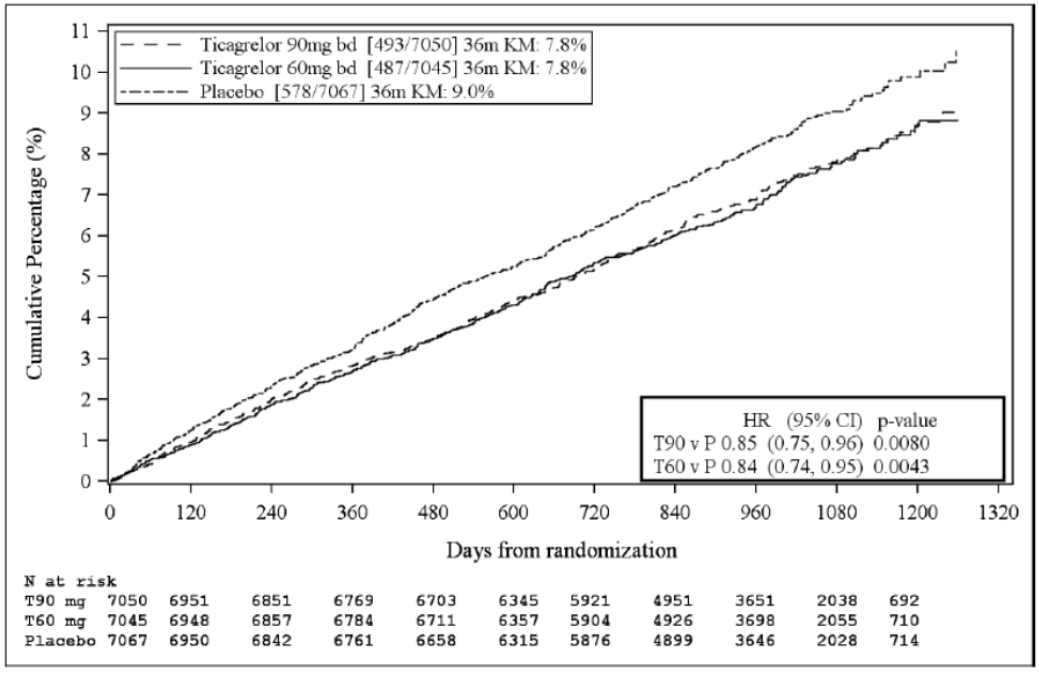
CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; RD = risk difference; TIC = ticagrelor 60 mg.

3.6.2 Cardiovascular mortality, myocardial infarction, or stroke

For the primary composite outcomes of time to CV mortality, MI, or stroke, 8.2% and 6.9% of patients (KM%, 9.0% and 7.8%) experienced one or more events in the placebo and ticagrelor 60 mg groups, respectively (Table 10, Figure 2). The differences were statistically significant for ticagrelor 60 mg (hazard ratio [HR] 0.84; 95% CI, 0.74 to 0.95) versus placebo (number needed to treat [NNT] = 79) (Figure 3, Figure 4).

Subgroup analyses based on region, history of more than one MI, multi-vessel coronary artery disease, prior PCI or stent implantation, or diabetes showed similar results to the overall population for the primary composite outcome (Appendix 4, Table 17). Subgroup analyses based on the time from qualifying MI showed no difference between ticagrelor 60 mg and placebo for patients who had MI two or more years prior to randomization (HR, 0.96; 95% CI, 0.79 to 1.17) compared with those with an MI two or fewer years prior (HR, 0.77; 95% CI, 0.66 to 0.90) (interaction term *P* value = 0.087). Ticagrelor 60 mg also showed no difference in efficacy versus placebo in patients whose prior ADP blocker treatment was more than 12 months before randomization (HR, 1.08; 95% CI, 0.82 to 1.42). This is in contrast with subgroups with more recent ADP blocker therapy (30 days to one year: HR, 0.81; 95% CI, 0.65 to 1.01; < 30 days: HR, 0.76; 95% CI, 0.62 to 0.93, interaction term *P* value = [redacted]) (Appendix 4, Table 17).

FIGURE 3: CUMULATIVE INCIDENCE OF THE PRIMARY EFFICACY COMPOSITE OUTCOME IN PEGASUS



bd = twice daily; CI = confidence interval; HR = hazard ratio; KM = Kaplan–Meier; m = months; P = placebo; T60 = ticagrelor 60 mg; T90 = ticagrelor 90 mg.
Source: Clinical Study Report.[6]

TABLE 10: KEY EFFICACY OUTCOMES

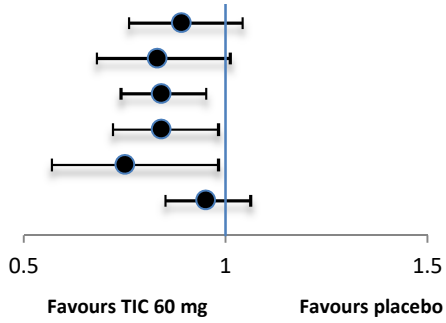
Outcome	PEGASUS		
Time to First Event	**Placebo N = 7,067**	**Ticagrelor 60 mg N = 7,045**	**Ticagrelor 90 mg N = 7,050**
All-cause Mortality			
n (%)	326 (4.6)	289 (4.1)	326 (4.6)
Kaplan–Meier % at 36 months	5.2	4.7	5.1
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		0.89 (0.76, 1.04)	1.00 (0.86, 1.16)
P value[a]		NS[b]	NS[b]
CV Mortality			
n (%)	210 (3.0)	174 (2.5)	182 (2.6)
Kaplan–Meier % at 36 months	3.4	2.9	2.9
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		0.83 (0.68, 1.01)	0.87 (0.71, 1.06)
P value[a]		0.068[c]	0.15[c]
CV Mortality, MI or Stroke			
n (%)	578 (8.2)	487 (6.9)	493 (7.0)
Kaplan–Meier % at 36 months	9.0	7.8	7.8
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		0.84 (0.74, 0.95)	0.85 (0.75, 0.96)
NNT (36 months)		79	[redacted]
P value[a]		0.0043	0.0080
MI			
n (%)	338 (4.8)	285 (4.0)	275 (3.9)
Kaplan–Meier % at 36 months	5.2	4.5	4.4
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		0.84 (0.72, 0.98)	0.81 (0.69, 0.95)
P value[a]		0.031[d]	0.010[d]
Stroke			
n (%)	122 (1.7)	91 (1.3)	100 (1.4)
RD (95% CI) versus placebo		[redacted]	[redacted]
Kaplan–Meier % at 36 months	1.9	1.5	1.6
HR (95% CI) versus placebo		0.75 (0.57 to 0.98)	0.82 (0.63 to 1.07)
P value[a]		0.034[d]	0.14[d]
CV Death, MI, Stroke, or TIMI Major Bleeding			
n (%)	618 (8.7)	585 (8.3)	618 (8.8)
Kaplan–Meier % at 36 months	9.6	9.3	9.8
RD (95% CI) versus placebo		NR	NR
HR (95% CI) versus placebo		0.95 (0.85, 1.06)	1.00 (0.90, 1.22)

Outcome	PEGASUS		
Time to First Event	**Placebo N = 7,067**	**Ticagrelor 60 mg N = 7,045**	**Ticagrelor 90 mg N = 7,050**
P value[a]		0.34[d]	0.96[d]

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NNT = number needed to treat; NR = not reported; NS = not satisfactory; RD = risk difference; TIMI = Thrombolysis in Myocardial Infarction.
[a] *P* values based on Cox proportional hazards model.
[b] Not statistically significant due to non-significant results in prior outcome (i.e., CV mortality) in the statistical testing procedure.
[c] No statistically significant differences were detected for CV mortality, the first secondary outcome in the statistical hierarchy; thus, no further statistical testing should be performed.
[d] Outside the hierarchical statistical testing procedure.
Source: Clinical Study Report.[6]

FIGURE 4: HAZARD RATIO FOR KEY OUTCOMES — TICAGRELOR 60 MG VERSUS PLACEBO

Outcome	HR (95% CI)
All-cause mortality	0.89 (0.76 to 1.04)[a]
CV mortality	0.83 (0.68 to 1.01)
CV mortality, MI, stroke	0.84 (0.74 to 0.95)
MI	0.84 (0.72 to 0.98)[b]
Stroke	0.75 (0.57 to 0.98)[b]
CV death, MI, stroke, TIMI major bleeding	0.95 (0.85 to 1.06)[b]



CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; TIC = ticagrelor 60 mg; TIMI = Thrombolysis in Myocardial Infarction.
[a] Not statistically significant due to non-significant results in prior outcome (i.e., CV mortality) in the statistical testing procedure.
[b] Outside the hierarchical statistical testing procedure.

3.6.3 Other cardiovascular events

There were fewer MI events (4.5 KM% versus 5.2 KM%) and fewer strokes (1.5 KM% versus 1.9 KM%) reported in the ticagrelor 60 mg group compared with the placebo group (Figure 2, Figure 4, Table 10). These events were outside the statistical hierarchy and thus are considered exploratory outcomes.

3.6.4 Cardiovascular mortality, myocardial infarction, stroke, or thrombosis in myocardial infarction major bleeding

An exploratory analysis of the net clinical benefit was conducted for the time to CV mortality, MI, stroke, or TIMI major bleeding. The KM% at 36 months was 9.6% and 9.3% for placebo and ticagrelor 60 mg (HR, 0.95; 95% CI, 0.85 to 1.06) (Figure 4, Table 10).

3.6.5 Stent thrombosis

[redacted]

[redacted]

TABLE 11: STENT THROMBOSIS

Outcome	PEGASUS		
Time to Stent Thrombosis	**Placebo**	**Ticagrelor 60 mg**	**Ticagrelor 90 mg**
Patients with Stent Prior to Randomization	N = 5,621	N = 5,658	N = 5,612
n (%)	48 (0.9)	40 (0.7)	30 (0.5)
Kaplan–Meier % at 36 months	[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo		[redacted]	[redacted]
P value		[redacted]	[redacted]

CI = confidence interval; HR = hazard ratio.
[a] Outside the hierarchical statistical testing procedure.
Source: Clinical Study Report.[6]

3.6.6 Health-related quality of life

The mean EQ-5D VAS scores ranged from [redacted] at baseline and from [redacted] at the end of treatment in the ticagrelor 60 mg and ticagrelor 90 groups compared to [redacted] for placebo, respectively (Table 12). No statistical testing was conducted; however, the differences between groups were small and not clinically important.

The mean EQ-5D index scores were similar at baseline ([redacted]) and at the end of treatment ([redacted]) for patients in the placebo and ticagrelor groups.

TABLE 12: EUROQOL 5-DIMENSIONS HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE

Outcome	PEGASUS					
	Placebo		**Ticagrelor 60 mg**		**Ticagrelor 90 mg**	
EQ-5D VAS	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Baseline	6,866	75.6 (17.3)	6,831	75.3 (17.5)	6,844	75.6 (17.0)
End of treatment	6,021	77.3 (15.9)	5,937	77.2 (15.8)	5,954	76.9 (16.0)
EQ-5D Index Score	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; SD = standard deviation; VAS = visual analogue scale.
Source: Clinical Study Report;[6] additional data supplied by the manufacturer.[8]

3.7 Harms

Only those harms identified in the review protocol are reported below (see section 2.2.1, Protocol). See Table 13 for detailed harms data.

Health Canada has approved the 60 mg dose only for this indication, so this review will focus on the safety of ticagrelor 60 mg twice daily compared with placebo.

3.7.1 Adverse events

Most patients (69% to 76%) reported one or more AEs during the PEGASUS trial (Table 13). Other than bleeding events, which are discussed in section 0, dyspnea was reported more frequently among patients who received ticagrelor 60 mg (12%) than placebo (4%). To note: a non-fatal event where the investigator submitted a cardiac ischemic event form or a cerebrovascular event form, and the events were adjudicated as "not a cardiac ischemic event," or "not a stroke or TIA," and "not an intracranial hemorrhage" were tabulated separately from other AEs (Appendix 4, Table 19). Most were cardiac-related events and the frequency of events varied from 5.0% in the placebo group to 4.2% to 4.6% in the ticagrelor groups.

3.7.2 Serious adverse events

The frequency of SAEs was similar in the ticagrelor and placebo groups (22%) (Table 13). Cardiac disorders, gastrointestinal disorders, infections, and neoplasms were the most commonly reported SAEs.

3.7.3 Withdrawals due to adverse events

More patients in the ticagrelor 60 mg group (16%) stopped treatment due to AEs compared with placebo (9%) (Table 13). Dyspnea and bleeding events were the most common AEs that led to treatment discontinuation.

3.7.4 Mortality

In the safety population, 3.1% and 2.5% of patients died of CV causes in the placebo and ticagrelor 60 mg groups, respectively (Table 13). The number of adjudicated non-CV deaths in the ticagrelor 60 mg (1.7%) and placebo groups (1.6%) was similar (Table 13).

TABLE 13: HARMS

Outcome	PEGASUS		
	Placebo N = 6,996	**Ticagrelor 60 mg N = 6,958**	**Ticagrelor 90 mg N = 6,988**
AEs[a]			
Patients with any AE, n (%)	4,837 (69)	5,268 (76)	5,327 (76)
Most common AEs:[b]			
Dyspnea	309 (4)	865 (12)	1,087 (16)
Epistaxis	156 (2)	422 (6)	511 (7)
Increased bruising	62 (1)	419 (6)	460 (7)
Contusion	108 (2)	349 (5)	376 (5)
Nasopharyngitis	349 (5)	347 (5)	340 (5)
Non-cardiac chest pain	374 (5)	341 (5)	316 (5)
Dizziness	261 (4)	290 (4)	304 (4)
Spontaneous hematoma	41 (< 1)	218 (3)	269 (4)
Hypertension	290 (4)	282 (4)	240 (3)
Bronchitis	180 (3)	187 (3)	217 (3)
Diarrhea	173 (3)	228 (3)	210 (3)
Back pain	226 (3)	226 (3)	195 (3)
Traumatic hematoma	45 (< 1)	160 (2)	193 (3)
SAE[a]			
Patients with any SAE, n (%)	1,511 (22)	1,499 (22)	1,514 (22)

Outcome	PEGASUS		
	Placebo N = 6,996	**Ticagrelor 60 mg N = 6,958**	**Ticagrelor 90 mg N = 6,988**
Most common SAE by system organ class:[b]			
Cardiac disorders	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	154 (2)	207 (3)	250 (4)
Infections and infestations	246 (4)	228 (3)	238 (3)
Neoplasms	[redacted]	[redacted]	[redacted]
WDAE[a]			
Treatment discontinuation due to AE, n (%)	596 (9)	1,117 (16)	1,306 (19)
Death[c]			
Death (including bleeding)	334 (4.8)	292 (4.2)	335 (4.8)
CV death	219 (3.1)	176 (2.5)	190 (2.7)
Sudden cardiac death	106 (1.5)	82 (1.2)	85 (1.2)
Acute MI	26 (0.4)	22 (0.3)	13 (0.2)
Hart failure or cardiogenic shock	22 (0.3)	18 (0.3)	24 (0.3)
Cerebrovascular event	21 (0.3)	17 (0.2)	21 (0.3)
Other CV cause	11 (0.2)	6 (0.1)	14 (0.2)
Presumed CV death	[redacted]	[redacted]	[redacted]
Non-CV death	[redacted]	[redacted]	[redacted]
Malignancy	[redacted]	[redacted]	[redacted]
Infection	24 (0.3)	25 (0.4)	31 (0.4)
Pulmonary failure	9 (0.1)	9 (0.1)	10 (0.1)
Hemorrhage (not intracranial)	5 (0.1)	5 (0.1)	6 (0.1)
Other	24 (0.6)	14 (0.2)	21 (0.3)

AE = adverse event; CV = cardiovascular; MI = myocardial infarction; SAE = serious adverse event; WDAE = withdrawal due to adverse events.
[a] On-treatment AEs occurring from the first dose up until 7 days after the last dose of study drug.
[b] Frequency > 3%.
[c] All adjudicated deaths, including those that were reported after the study end date or after withdrawal of consent.
Source: Clinical Study Report.[6]

3.7.5 Notable Harms — Bleeding

Bleeding events were reported in 29% and 12% of patients in the ticagrelor 60 mg and placebo groups, respectively (Table 14). The frequency of serious bleeding AEs and bleeding leading to study drug discontinuation was also higher in the ticagrelor than placebo groups.

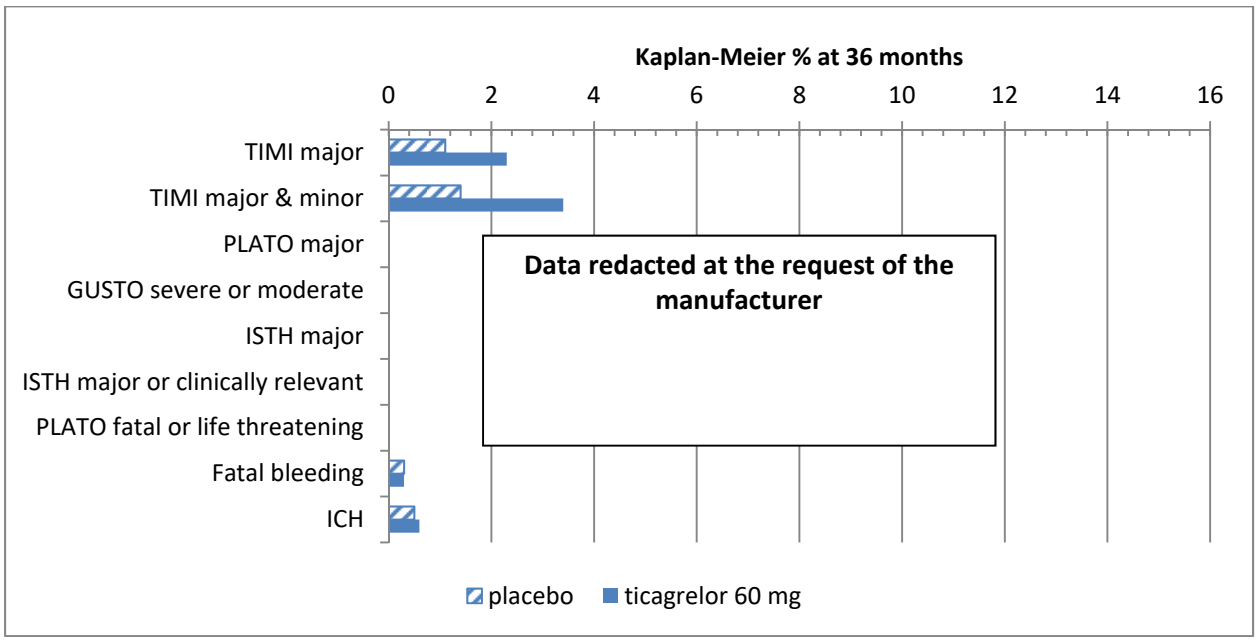
TABLE 14: NOTABLE HARMS — BLEEDING

Outcome	PEGASUS		
	Placebo N = 6,996	**Ticagrelor 60 mg N = 6,958**	**Ticagrelor 90 mg N = 6,988**
Notable Harms			
Bleeding			
Any bleeding event, n (%)[a]	807 (12)	2,028 (29)	2,256 (32)
Bleeding SAE, n (%)	[redacted]	[redacted]	[redacted]
Bleeding leading to discontinuation of study drug, n (%)	88 (1.3)	355 (5.1)	454 (6.5)

SAE = serious adverse event.
[a] Any bleeding-related adverse events documented by the investigator, including unadjudicated minimal bleeding, excluding events adjudicated as not a bleeding event.
Source: Clinical Study Report.[6]

Adjudicated bleeding events were classified according to the TIMI, PLATO, GUSTO, and ISTH standard definitions (Appendix 4, Table 21). While the absolute risk of bleeding varied depending on the definition used (Figure 5), the relative risk of bleeding was consistently higher for ticagrelor 60 mg (HR range: 2.3 to [redacted]) compared with placebo (Table 15, Figure 6).

FIGURE 5: ABSOLUTE RISK OF BLEEDING — TICAGRELOR 60 MG VERSUS PLACEBO



ICH = intracranial hemorrhage; ISTH = International Society on Thrombosis and Haemostasis; TIMI = Thrombolysis in Myocardial Infarction.

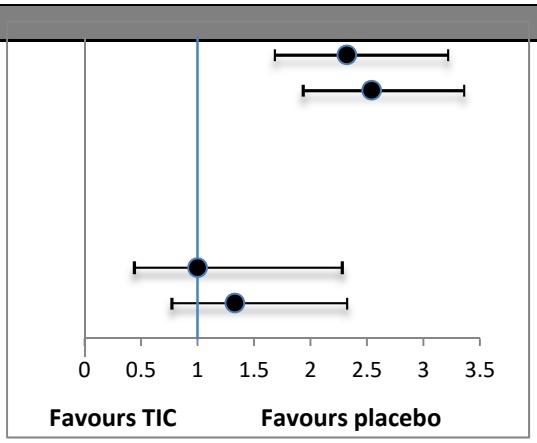
Estimates of the number needed to harm (NNH) showed that for every 81 patients treated for three years with ticagrelor 60 mg twice daily plus ASA, one patient would experience an additional TIMI major bleed, compared with ASA alone (RD [redacted]) (Table 15). Kaplan–Meier curves showed a constant risk of TIMI major bleeding over time (Figure 7). The frequency of procedural-related TIMI major bleeding was similar across treatment groups but spontaneous and trauma-related TIMI major bleeding were more

frequent in the ticagrelor than placebo groups. Gastrointestinal bleeding was the most common site of TIMI major bleeding. Among patients who reported TIMI major bleeding, [redacted] required a new or prolonged hospitalization in connection with the bleeding.

Fatal or life-threatening bleeding was reported more frequently in the ticagrelor than placebo groups (KM% ticagrelor 60 mg: 2.4%; placebo: 1.1%) (Table 15). Twelve patients in the placebo group had fatal bleeding compared with 11 in the ticagrelor 60 mg group. Intracranial hemorrhage was reported in 23 and 28 patients in the placebo and ticagrelor 60 mg groups, respectively (KM%: 0.5% and 0.6%).

FIGURE 6: HAZARD RATIO OF BLEEDING RISK — TICAGRELOR 60 MG VERSUS PLACEBO

Bleeding Outcome	HR (95% CI)
TIMI major	2.32 (1.68 to 3.21)
TIMI major or minor	2.54 (1.93 to 3.35)
PLATO major	[redacted]
GUSTO severe or moderate	[redacted]
ISTH major	[redacted]
PLATO fatal or life-threatening	[redacted]
Fatal bleeding	1.00 (0.44 to 2.27)
ICH	1.33 (0.77 to 2.31)



CI = confidence interval; HR = hazard ratio; ICH = intracranial hemorrhage; ISTH = International Society on Thrombosis and Haemostasis; TIC = ticagrelor 60 mg; TIMI = Thrombolysis in Myocardial Infarction.

An increased risk of TIMI major bleeding was observed for ticagrelor 60 mg versus placebo across subgroups based on region, history of more than one MI, multi-vessel coronary artery disease, prior PCI or stent implantation, diabetes, time since qualifying MI, or time since previous ADP receptor blocker treatment (HR range: 1.6 to 3.8) (Appendix 4, Table 18).

TABLE 15: ADJUDICATED BLEEDING EVENTS

Outcome	PEGASUS		
Time to First Event[a]	**Placebo N = 6,996**	**Ticagrelor 60 mg N = 6,958**	**Ticagrelor 90 mg N = 6,988**
TIMI Major Bleeding			
n (%)	54 (0.8)	115 (1.7)	127 (1.8)
Kaplan–Meier % at 36 months	1.1	2.3	2.6
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		2.32 (1.68 to 3.21)	2.69 (1.96 to 3.70)
P value		< 0.0001[b]	< 0.0001[b]
NNH (36 months)		81	65
TIMI Major or Minor Bleeding			
n (%)	72 (1.0)	168 (2.4)	192 (2.7)
Kaplan–Meier % at 36 months	1.4	3.4	3.9

Outcome	PEGASUS		
Time to First Event[a]	**Placebo N = 6,996**	**Ticagrelor 60 mg N = 6,958**	**Ticagrelor 90 mg N = 6,988**
RD (95% CI) versus placebo		[redacted]	[redacted]
HR (95% CI) versus placebo		2.54 (1.93 to 3.35)	3.05 (2.32 to 4.00)
P value		< 0.0001[b]	< 0.0001[b]
NNH (36 months)		[redacted]	[redacted]
PLATO Major Bleeding			
n (%)	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months	[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo		[redacted]	[redacted]
P value		[redacted]	[redacted]
GUSTO Severe or Moderate Bleeding			
n (%)	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months	[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo		[redacted]	[redacted]
P value		[redacted]	[redacted]
ISTH Major Bleeding			
n (%)	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months	[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo		[redacted]	[redacted]
P value		[redacted]	[redacted]
ISTH Major or Minor Clinically Relevant Bleeding			
n (%)	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months	[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo		[redacted]	[redacted]
P value		[redacted]	[redacted]
Fatal Bleeding[d]			
n (%)	12 (0.2)	11 (0.2)	6 (0.1)
Kaplan–Meier % at 36 months	0.3	0.3	0.1
HR (95% CI) versus placebo		1.00 (0.44 to 2.27)	0.58 (0.22 to 1.54)
P value		1.00[b]	0.27[b]
Fatal or Life-Threatening (PLATO)[e]			
n (%)	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months	[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo		[redacted]	[redacted]
P value		[redacted]	[redacted]
Intracranial Hemorrhage			
n (%)	23 (0.3)	28 (0.4)	29 (0.4)
Kaplan–Meier % at 36 months	0.5	0.6	0.6
HR (95% CI) versus placebo		1.33 (0.77 to 2.31)	1.44 (0.83 to 2.49)

Outcome	PEGASUS		
Time to First Event[a]	**Placebo N = 6,996**	**Ticagrelor 60 mg N = 6,958**	**Ticagrelor 90 mg N = 6,988**
P value		0.31[b]	0.19[b]

CI = confidence interval; HR = hazard ratio; ISTH = International Society on Thrombosis and Haemostasis; NNH = number needed to harm; NNT = number needed to treat; RD = risk difference; TIMI = Thrombolysis in Myocardial Infarction.
[a] Adverse events with an onset date on or after the date of first dose and up to and including 7 days following the date of last dose of study drug.
[b] Exploratory outcome. *P* value based on Cox proportional hazards model.
[c] Calculated by CADTH (NNT = 1/RD).
[d] Fatal bleeding was adjudicated as an event where bleeding led directly to death within 7 days.
[e] Fatal or life-threatening bleeding events (including intracranial hemorrhage) according to PLATO criteria.
Source: Clinical Study Report,[6] CADTH Common Drug Review submission,[7] additional data supplied by manufacturer.[8]

FIGURE 7: CUMULATIVE INCIDENCE OF THROMBOLYSIS IN MYOCARDIAL INFARCTION MAJOR BLEEDING IN PEGASUS

[Confidential data regarding cumulative incidence of TIMI major bleeding were removed at the manufacturer's request.]

bd = twice daily; CI = confidence interval; HR = hazard ratio; KM = Kaplan–Meier; m = months; P = placebo; T60 = ticagrelor 60 mg; T90 = ticagrelor 90 mg; TIMI = Thrombolysis in Myocardial Infarction.
Source: Clinical Study Report.[6]

Notable Harms — Other

Dyspnea-related events were reported more frequently among patients who received ticagrelor 60 mg than placebo (14% versus 6%) and were the reason for treatment discontinuation for 4% versus 1% of patients, respectively (Table 16).

The frequency of bradyarrhythmic AEs was similar in the ticagrelor 60 mg and placebo groups (1.7% and 1.5%); however, AEs that were possibly related to bradyarrhythmia (e.g., dizziness, hypotension, syncope) were reported more frequently in the ticagrelor 60 mg (8.4%) than placebo (7.4%) group (Table 16). Of note: the PEGASUS study excluded patients who were at risk of bradycardic events.

The Food and Drug Administration (FDA) identified gout as a possible AE of interest.[17] Gout or gouty arthritis was reported in 115, 101, and 74 patients on ticagrelor 90 mg, ticagrelor 60 mg, and placebo, respectively, corresponding to KM% of 2.3%, 2.0%, and 1.5% at 36 months.

TABLE 16: NOTABLE HARMS — OTHER

Outcome	PEGASUS		
	Placebo N = 6,996	**Ticagrelor 60 mg N = 6,958**	**Ticagrelor 90 mg N = 6,988**
Notable Harms			
Dyspnea			
Any dyspnea event, n (%)[a]	382 (5.5)	986 (14.2)	1,204 (17.2)
Dyspnea, event rate per 100 PY[ab]	[redacted]	[redacted]	[redacted]
Dyspnea, SAE, n (%)[a]	8 (0.1)	22 (0.3)	22 (0.3)
Dyspnea leading to discontinuation of study drug, n (%)[a]	51 (0.7)	296 (4.3)	430 (6.2)
Bradyarrhythmia			
Any bradyarrhythmic AE, n (%)[c]	105 (1.5)	121 (1.7)	105 (1.5)
Bradyarrhythmic SAE, n (%)[c]	29 (0.4)	33 (0.5)	31 (0.4)
Bradyarrhythmia leading to discontinuation of study drug, n (%)[c]	2 (0.0)	4 (0.1)	3 (0.0)

AE = adverse event; PY = patient-year; SAE = serious adverse event.
[a] Includes AEs with one of the five preferred terms: dyspnea, dyspnea at rest, dyspnea exertional, dyspnea paroxysmal nocturnal, and nocturnal dyspnea.
[b] Number of patients with dyspnea divided by the total duration of treatment across all patients in a given group, multiplied by 100.
[c] Includes 24 bradyarrhythmic-related AEs, of which bradycardia, sinus bradycardia, and first- and second-degree atrioventricular block were most commonly reported.
Source: Clinical Study Report.[6]

4. DISCUSSION

4.1 Summary of available evidence

One DB RCT met the inclusion criteria. PEGASUS tested the superiority of ticagrelor 90 mg and 60 mg twice daily versus placebo (as add-on therapy to low-dose ASA) in patients older than 50 years with a history of MI (one year to three years prior to randomization), and who were at high risk of atherothrombotic events (N = 21,162). The primary outcome was time to first occurrence of CV death, MI, or stroke. PEGASUS was an event-driven trial and patients were followed for a minimum of 12 months and until at least 1,360 primary efficacy events occurred. The available evidence was limited to a single RCT, which has some limitations in terms of external validity.

4.2 Interpretation of Results

4.2.1 Efficacy

In the PEGASUS study, a statistically significant difference was detected between ticagrelor 60 mg twice daily + ASA versus placebo + ASA, for the primary composite outcome of time to CV mortality, MI, or stroke (HR, 0.84; 95% CI, 0.74 to 0.95). Thus, for every 79 patients treated with dual antiplatelet therapy for up to three years in this population, one patient would avoid a major CV event, versus ASA alone. No significant differences were detected between groups in time to CV mortality or all-cause mortality, which were secondary outcomes in PEGASUS. The frequency of MI (4.5 KM% versus 5.2 KM%) and stroke (1.5 KM% versus 1.9 KM%) were lower in the ticagrelor 60 mg versus placebo groups. [redacted].

Subgroup analyses based on region, history of more than one MI, multi-vessel coronary artery disease, prior PCI or stent implantation, or diabetes showed similar results to the overall population for the primary composite outcome. However, subgroup analyses based on the time from qualifying MI showed no difference between ticagrelor 60 mg and placebo for the primary composite outcome in patients who had MI two or more years prior to randomization, unlike those with an MI less than two years previously, although the interaction term did not reach statistical significance (*P* = 0.087). Ticagrelor 60 mg also showed no statistically significant difference for the primary outcome in patients whose last ADP blocker was > 12 months prior to randomization, in contrast with subgroups with more recent ADP blocker therapy (interaction term *P* value = [redacted]). A similar pattern was observed for the ticagrelor 90 mg treatment group. The FDA commented that these subgroup effects have biological plausibility, and suggested that those with an MI more than two years prior or those who stopped ADP therapy for more than 12 months may not benefit from restarting dual antiplatelet therapy with ticagrelor.[17] The trial was designed so that patients who had a recent major CV event were excluded from the study, so for patients who have remained stable during an extended time off dual antiplatelet therapy, there may be limited benefits to re-initiating ticagrelor. Health Canada does not recommend re-initiating dual antiplatelet therapy with ticagrelor if more than two years have passed since the patient's spontaneous MI, or more than one year after stopping previous ADP receptor antagonist treatment.[4] The treatment duration should not exceed three years.[4] Of note: there was overlap between patients with an MI more than two years prior, and those who received an ADP blocker more than 12 months ago. Caution is

warranted in interpreting the subgroup data, considering the number of subgroups tested and the lack of statistically significant interaction terms.

A previous secondary prevention trial showed no clear benefit of long-term dual antiplatelet therapy. The CHARISMA trial (N = 15,603) found no statistically significant difference between clopidogrel plus ASA and placebo plus ASA (median follow-up 28 months) in the risk of CV death, MI, or stroke (relative risk [RR], 0.95; 95% CI, 0.83 to 1.05; *P* = 0.22).[18] The inclusion criteria, however, were more broad than PEGASUS, and included patients with either clinically evident coronary, cerebrovascular, or peripheral vascular disease, or those with multiple atherothrombotic risk factors. Post-hoc subgroup analysis of CHARISMA suggested a benefit with dual antiplatelet therapy for patients with prior MI (N = 3,846).[19] In the CHARISMA trial, GUSTO severe (1.7% versus 1.3%) and moderate bleeding (2.1% versus 1.3%) was reported more frequently in patients on dual antiplatelet therapy versus ASA alone.[18] A recent meta-analysis that examined longer-term dual antiplatelet therapy (> 1 year) versus ASA alone in patients with prior MI, or PCI patients with acute coronary syndrome, found a reduced risk of major CV events but an increased risk of major bleeding.[9] This meta-analysis included results from the PEGASUS study and subgroup data from CHARISMA, DAPT, PRODIGY, ARCTIC-Interruption and DES-LATE RCTs.[9] Another recent meta-analysis did not demonstrate clear benefits to extending dual antiplatelet therapy with clopidogrel plus ASA therapy beyond one year after an acute coronary syndrome occurrence.[20]

4.2.2 Harms

Most patients in the PEGASUS study (69% to 76%) reported one or more AEs, including bleeding events (29% versus 12%) and dyspnea (14% versus 6%) which were reported more frequently among patients who received ticagrelor 60 mg than placebo. More patients stopped treatment due to AEs in the ticagrelor 60 mg group than the placebo group (16% versus 9%); however, the frequency of SAEs was the same in the treatment groups (22%).

The most notable AE was the increased risk of bleeding with ticagrelor versus placebo. Ticagrelor 60 mg twice daily was associated with an increased risk of adjudicated bleeding events based on TIMI, PLATO, GUSTO, and ISTH criteria (HR range: 2.3 to [redacted]). The absolute risk of bleeding, however, depends on the definition used, and ranged from 2.3 KM% (TIMI major bleeding) to [redacted] (ISTH major or minor clinically relevant bleeding) in the ticagrelor 60 mg group. The risk of bleeding appeared to be constant over time, and to be increased across different subgroups of patients. The risk of intracranial hemorrhage or fatal bleeding was low, and numerically more patients in the ticagrelor 60 mg group experienced an intracranial hemorrhage compared with placebo. However, we are unable to draw any conclusions with regard to these events given that the study was not powered to test for differences between treatments. Although the focus of this report is on the 60 mg ticagrelor dose, the 90 mg dose also showed an elevated risk of TIMI, PLATO, GUSTO, and ISTH bleeding compared with placebo (HR range: 2.6 to [redacted]), with absolute risks of bleeding that were numerically higher than the 60 mg ticagrelor dose. This increased risk of bleeding was present even though patients at increased risk of bleeding, with a history of intracranial hemorrhage, or a gastrointestinal bleed in the past six months, were excluded from the trial.

The net clinical benefit does not show a clear advantage for ticagrelor plus ASA versus ASA alone based on the analysis of time to CV mortality, MI, stroke, or TIMI major bleeding (HR, 0.95; 95% CI, 0.85 to 1.06). The absolute risk reductions in major CV events ([redacted]) appear to be offset by a similar absolute increase in major bleeding events ([redacted]). TIMI major bleeding is a significant clinical event (defined as fatal bleeding, intracranial hemorrhage, or hemorrhage associated with a drop in hemoglobin ≥ 50 g/L) which would most often require hospitalization, blood transfusion, and other interventions to identify and control the source of bleeding. To patients, these events may be life-threatening and for some, may

have long-term sequelae. The available data suggest that additional research is needed to identify which patients are most likely to benefit from long-term dual antiplatelet therapy, without substantial increased risk of bleeding.

4.3 Potential Place in Therapy[1]

The information in this section is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Patients with a prior coronary artery event have a high rate of recurrent acute coronary syndrome — as high as 10% per year according to some studies,[21-23] even after treatment with ASA and clopidogrel in combination.[24] Not surprisingly, there is an attendant 10% increase in medical costs associated with such episodes.[25] Subsequent events are obviously at least partly due to disease progression and this has been the driver in seeking more intensive treatment following an acute coronary syndrome occurrence. But other important contributors include patient non-compliance with secondary prevention medications as well as underlying patient risk and the extent that such risk can be modified, in the event that it can be.[26]

A recent meta-analysis of 14 randomized trials with more than 69,000 patients[20] found that the combination of ASA and clopidogrel did not appear to influence outcome more than 12 months beyond an acute coronary syndrome event, whether or not treated with PCI and stenting. However, there were insufficient data to comment on the effect of dual antiplatelet therapy involving other P2Y12 inhibitors. The PEGASUS-TIMI 54 trial[15] showed that dual antiplatelet therapy using ticagrelor in addition to low-dose ASA effectively reduces the risk of subsequent coronary events, albeit at a comparable increased risk of major bleeds. The clinical expert consulted for this review noted that, given the relatively equal balance between efficacy and safety, rather than the clear preponderance of the former over the latter, concerns might be raised about the unselected use of ticagrelor in all patients following acute coronary syndrome.

Subgroup analysis of the PEGASUS-TIMI 48 trial has suggested that there are select patients in whom there is clear benefit and others for whom there is not.[27,28] Accordingly, careful risk stratification has been advocated as a means of identifying those patients who might benefit most from ticagrelor given that its benefit in terms of subsequent coronary events is otherwise equally balanced by its corresponding risk of major bleeds.[29,30] In the meantime, a recent non–ST elevation acute coronary syndrome guidelines update by the European Society of Cardiology[31] now includes a recommendation (Class IIb, Level of Evidence A) that dual antiplatelet therapy beyond one year "may be considered after careful assessment of the ischaemic and bleeding risks of the patient."

The clinical expert noted that certain important questions remain regarding the potential benefits of dual antiplatelet therapy with ASA and ticagrelor in select patients. These include: 1) whether such therapy should nonetheless have some time limit on administration, or be open ended and thus lifelong in its use; 2) the not insignificant side effects (most notably dyspnea) that might adversely affect patient adherence and hence event outcome; 3) the increase to an already high pill burden that might have an additional negative impact on adherence; 4) physician reluctance to prescribe long-term dual antiplatelet therapy in view of the bleeding risk, an outcome so feared that it has negatively affected the long-term administration of other antithrombotic drugs — most notably, the prescribing of oral anticoagulants in the thromboembolic prophylaxis of atrial fibrillation despite oral anticoagulants having

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

shown relatively greater benefit for this indication than has dual antiplatelet therapy with ticagrelor in acute coronary syndrome; 5) both the systemic and societal costs, which will not be insignificant. Insight into all these issues is unlikely to be available until phase 4 study results are available; and these, in turn, will require that the drug come to market with the expanded indication being sought in order to provide the amount of data necessary to make any phase 4 findings sufficiently robust.

5. CONCLUSIONS

Ticagrelor 60 mg twice daily plus ASA appears to have contributed to a reduced risk in CV death, MI, or stroke over a three-year period, compared with ASA alone, among patients with a history of MI and additional atherothrombotic risk factors. No clinically important differences were observed in terms of CV mortality, all-cause mortality, or HRQoL with ticagrelor 60 mg plus ASA over ASA alone, based on data from a single RCT. No conclusions can be made with regard to the impact of ticagrelor on stent thrombosis, fatal bleeding, or non-fatal intracranial hemorrhage, due to the low incidence of events.

Ticagrelor 60 mg plus ASA was associated with an increased frequency of dyspnea and clinically important major bleeding events, versus ASA alone. The net clinical benefit did not show a clear advantage for ticagrelor plus ASA versus ASA alone based on the analysis of time to CV mortality, MI, stroke, or TIMI major bleeding. The clinical importance of the reduction in major CV events needs to be evaluated, however, relative to the observed increased risk of major bleeding.

As the median treatment duration in the trial was 29 months, the risks and benefits for longer-term treatment durations are uncertain.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief description of patient group(s) supplying input

Input was received from one patient group. The Heart and Stroke Foundation of Canada (HSF) is a national volunteer-based charity run by 125,000 volunteers that supports heart and stroke research and runs health promotion and advocacy programs across the country with the goal of reducing the impact of and eliminating heart disease and stroke. Over the last 60 years, the HSF has invested more than $1.39 billion in heart and stroke research. Conflict of interest declarations include the receipt of unrestricted financial support from pharmaceutical companies including AstraZeneca. No conflict was declared in the preparation of the submission.

2. Condition-related information

Information on condition impact to patients and caregivers was collected via an online survey that was advertised using posts through Facebook and pop-ups on heart attack information pages of the HSF website. Of the 239 individuals who responded to the survey, 221 indicated that they had been told by a health care professional that they had had a heart attack, and 26 indicated that they were a caregiver for someone who had had a heart attack. Information was also gathered through literature searches, Statistics Canada, the Public Health Agency of Canada, HSF health information, and guidelines and policies from credible organizations.

In 2012, almost 14,000 Canadians died from a heart attack and each year more than 305,000 are hospitalized for heart disease despite progress in surgical procedures, drug therapies, and preventative measures. Of 221 respondents identified as a heart attack survivor (175 having had their most recent heart attack within the last five years), 187 patients responded to the question “How has having a heart attack affected your day-to-day life?” with the following most common responses: having to take medication at specific times (108 patients); taking medication multiple times a day (86); frequent visits to a health care provider (75); time off work (50); managing their condition with other forms of therapy (49); and not affecting day-to-day life (38). Seventy-three patients indicated that they were unable to do certain activities as a result of having a heart attack, including any strenuous activity (25); lifting or carrying objects (15); walking long distances or uphill (13); and routine day-to-day activities such as housework (11). Symptoms experienced as a result of their heart attack included: fatigue (67); angina and/or pain (42); memory loss and cognitive impairment (33); swelling and fluid retention (13); and shortness of breath (9). One patient described living with heart failure due to a heart attack as having “completely changed my life.”

Caregivers (n = 26) of heart attack survivors are also affected due to the need to transport the patient to the health care provider (10), having to take time off work (9), and needing to provide additional care due to side effects from treatment (8). Caregivers also stated that they were more anxious or stressed (11), had less freedom (8), and felt overwhelmed (8).

3. Current therapy-related information

Of the 221 respondents who had survived a heart attack, 210 reported that they had been prescribed medication to prevent a second heart attack and to manage the following: high blood pressure (166), high blood cholesterol (181), and diabetes (25). The majority of patients (200) were on antiplatelet or blood thinner medications such as acetylsalicylic acid (ASA), clopidogrel, prasugrel, ticagrelor, and/or ticlopidine. Other prescribed medications included antidepressants, beta blockers, heart rate–lowering medication, and anti-seizure medications.

When asked the question "Other than being cured, what would the best course of treatment look like for you?", 18 patients expressed a desire for a reduction in medications, no medications, and/or medications with few side effects.

4. Expectations about the drug being reviewed

Eighty-seven respondents indicated they had taken ticagrelor as part of a clinical trial or been prescribed the medication by their health care provider, with 42 patients currently on the medication. Of the patients who had ever previously used ticagrelor (n = 84), 29 reported that ticagrelor is helping control their condition, 50 reported that they were unsure whether it was helping, and five felt that it did not help control their condition. Of 83 patients, 35 indicated that they did not experience any side effects with ticagrelor, 24 reported shortness of breath, 10 reported headaches, and 13 reported experiencing nose bleeds.

Of the 87 patients who had taken ticagrelor, 70 patients indicated that they had also taken ASA. When compared with ASA, 16 patients felt that they experienced worse shortness of breath with ticagrelor, eight patients felt that headaches were worse with ticagrelor, nine patients felt that nosebleeds were worse with ticagrelor, 14 felt that other bleeding was worse with ticagrelor, and eight patients felt that the side effects on ticagrelor were worse. In addition, 23 patients felt that ticagrelor was less affordable than ASA.

Of the 87 patients who had taken ticagrelor, 14 indicated that they had also taken clopidogrel. Compared with clopidogrel, nine patients felt that they experienced worse shortness of breath with ticagrelor, four patients felt that headaches were worse with ticagrelor, three patients felt that nosebleeds were worse with ticagrelor, and three patients felt that other bleeding was worse with ticagrelor. In addition, three patients felt that ticagrelor was less affordable than clopidogrel.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 18, 2016
Alerts:	Monthly search updates until July 20, 2016 (date of CDEC meeting)
Study Types:	randomized controlled trials; controlled clinical trials
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

#	Searches
1	(ticagrelor* or Brilinta* or Brilique* or Possia* or AZD6140 or AZD 6140 or 274693-27-5 or GLH0314RVC or Brylinta* or Tiglor*).ti,ab,ot,kw,kf,hw,rn,nm.
2	1 use pmez
3	*Ticagrelor/ or (ticagrelor* or Brilinta* or Brilique* or Possia* or AZD6140 or AZD 6140 or 274693-27-5 or UNII-GLH0314RVC or Brylinta* or Tiglor*).ti,ab.
4	3 use oemezd

MULTI-DATABASE STRATEGY	
#	**Searches**
5	2 or 4
6	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.
7	Randomized Controlled Trial/
8	exp Randomized Controlled Trials as Topic/
9	"Randomized Controlled Trial (topic)"/
10	Controlled Clinical Trial/
11	exp Controlled Clinical Trials as Topic/
12	"Controlled Clinical Trial (topic)"/
13	Randomization/
14	Random Allocation/
15	Double-Blind Method/
16	Double Blind Procedure/
17	Double-Blind Studies/
18	Single-Blind Method/
19	Single Blind Procedure/
20	Single-Blind Studies/
21	Placebos/
22	Placebo/
23	Control Groups/
24	Control Group/
25	(random* or sham or placebo*).ti,ab,hw,kf,kw.
26	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
27	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
28	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
29	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
30	allocated.ti,ab,hw.
31	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
32	or/6-31
33	5 and 32
34	33 not conference abstract.pt.
35	remove duplicates from 34

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	March 2016
Keywords:	Brilinta (ticagrelor)
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Magnani G, Storey RF, Steg G, Bhatt DL, Cohen M, Kuder J, et al. Efficacy and safety of ticagrelor for long-term secondary prevention of atherothrombotic events in relation to renal function: insights from the PEGASUS-TIMI 54 trial. Eur Heart J. 2016 Jan 21;37(4):400-8.	Not a subgroup of interest
Bonaca MP, Bhatt DL, Steg PG, Storey RF, Cohen M, Im K, et al. Ischaemic risk and efficacy of ticagrelor in relation to time from P2Y12 inhibitor withdrawal in patients with prior myocardial infarction: insights from PEGASUS-TIMI 54. Eur Heart J. 2015 Oct 21.	Not a subgroup of interest
Spinar J, Spinarova L, Vitovec J. PEGASUS - Ticagrelor in secondary prevention on patients after a myocardial infarction. Vnitr Lek. 2015 Jun;61(6):511-5. In Czech.	Duplicate (non-English report on PEGASUS trial)

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 17: EXPLORATORY SUBGROUP ANALYSES OF PRIMARY OUTCOME

Subgroup	PEGASUS			
Time to CV Death, MI, or Stroke	**Total N**	**Placebo N = 7,067**	**Ticagrelor 60 mg N = 7,045**	**Ticagrelor 90 mg N = 7,050**
Region				
Interaction term *P* value			0.83	1.00
North America	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		9.8	7.8	9.1
HR (95% CI) versus placebo			0.75 (0.57 to 0.99)	0.86 (0.66 to 1.13)
Europe and South Africa	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		9.0	7.5	7.6
HR (95% CI) versus placebo			0.85 (0.72 to 0.99)	0.85 (0.73 to 1.00)
Asia and Australia	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		6.9	7.1	6.1
HR (95% CI) versus placebo			0.90 (0.60 to 1.34)	0.82 (0.54 to 1.23)
South America	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		9.8	9.9	8.6
HR (95% CI) versus placebo			0.90 (0.65 to 1.24)	0.83 (0.60 to 1.16)
History of > 1 MI				
Interaction term *P* value			0.88	0.54
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		15.2	13.7	14.7
HR (95% CI) versus placebo			0.85 (0.68 to 1.06)	0.90 (0.72 to 1.13)
No	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		7.8	6.6	6.5
HR (95% CI) versus placebo			0.83 (0.72 to 0.96)	0.83 (0.72 to 0.96)
Multi-Vessel Coronary Artery Disease				
Interaction term *P* value			0.55	0.79
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		9.4	7.8	8.1
HR (95% CI) versus placebo			0.81 (0.70 to 0.95)	0.84 (0.72 to 0.98)
No	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		8.6	7.7	7.5
HR (95% CI) versus placebo			0.88 (0.72 to 1.06)	0.87 (0.72 to 1.05)
History of PCI				
Interaction term *P* value			0.78	0.87
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		8.1	6.9	7.2
HR (95% CI) versus placebo			0.83 (0.72 to 0.96)	0.85 (0.74 to 0.98)
No	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		13.5	12.0	11.0
HR (95% CI) versus placebo			0.87 (0.68 to 1.10)	0.84 (0.66 to 1.06)

Subgroup	PEGASUS			
Time to CV Death, MI, or Stroke	**Total N**	**Placebo N = 7,067**	**Ticagrelor 60 mg N = 7,045**	**Ticagrelor 90 mg N = 7,050**
History of Coronary Stent Implantation				
Interaction term *P* value			[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo			[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo			[redacted]	[redacted]
Diabetes				
Interaction term *P* value			0.96	0.97
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		11.6	10.0	10.1
HR (95% CI) versus placebo			0.83 (0.69 to 1.00)	0.85 (0.71 to 1.03)
No	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		7.8	6.7	6.8
HR (95% CI) versus placebo			0.84 (0.72 to 0.98)	0.85 (0.73 to 0.99)
Time From Qualifying MI to Randomization				
Interaction term *P* value			0.087	0.58
< 2 years	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		9.7	7.8	8.1
HR (95% CI) versus placebo			0.77 (0.66 to 0.90)	0.83 (0.71 to 0.96)
≥ 2 years	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		7.9	7.8	7.3
HR (95% CI) versus placebo			0.96 (0.79 to 1.17)	0.89 (0.72 to 1.08)
Time Since Previous Treatment with ADP Receptor Blocker				
Interaction term *P* value			[redacted]	[redacted]
< 30 days	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		10.0	8.1	7.3
HR (95% CI) versus placebo			0.76 (0.62 to 0.93)	0.69 (0.56 to 0.85)
30 days to 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		8.7	7.1	8.1
HR (95% CI) versus placebo			0.81 (0.65 to 1.01)	0.91 (0.73 to 1.13)
≥ 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		6.8	7.0	6.2
HR (95% CI) versus placebo			1.08 (0.82 to 1.42)	0.96 (0.72 to 1.26)

ADP = adenosine diphosphate; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary revascularization.
Source: Clinical Study Report.[6]

TABLE 18: EXPLORATORY SUBGROUP ANALYSES OF THROMBOLYSIS IN MYOCARDIAL INFARCTION MAJOR BLEEDING

Subgroup	PEGASUS			
Time to TIMI Major Bleeding	**Total N**	**Placebo N = 7,067**	**Ticagrelor 60 mg N = 7,045**	**Ticagrelor 90 mg N = 7,050**
Region				
Interaction term *P* value			0.65	0.92
North America	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.4	3.6	3.1
HR (95% CI) versus placebo			2.67 (1.36 to 5.23)	2.33 (1.16 to 4.65)
Europe and South Africa	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		0.9	1.7	2.2
HR (95% CI) versus placebo			2.09 (1.31 to 3.32)	2.75 (1.76 to 4.31)
Asia and Australia	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.4	3.7	3.0
HR (95% CI) versus placebo			3.23 (1.45 to 7.18)	2.37 (1.02 to 5.50)
South America	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.1	2.0	3.5
HR (95% CI) versus placebo			1.60 (0.61 to 4.21)	3.39 (1.44 to 7.97)
History of > 1 MI				
Interaction term *P* value			0.20	0.57
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		0.7	3.2	2.3
HR (95% CI) versus placebo			3.82 (1.65 to 8.87)	3.46 (1.46 to 8.19)
No	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.1	2.1	2.7
HR (95% CI) versus placebo			2.10 (1.48 to 2.99)	2.58 (1.83 to 3.64)
Multi-vessel Coronary Artery Disease				
Interaction term *P* value			0.26	0.96
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.1	2.6	2.5
HR (95% CI) versus placebo			2.68 (1.77 to 4.07)	2.66 (1.75 to 4.05)
No	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.0	1.9	2.8
HR (95% CI) versus placebo			1.83 (1.09 to 3.07)	2.72 (1.67 to 4.43)
History of PCI				
Interaction term *P* value			0.55	0.68
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.1	2.4	2.6
HR (95% CI) versus placebo			2.42 (1.70 to 3.44)	2.76 (1.95 to 3.91)
No	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.0	1.6	2.5
HR (95% CI) versus placebo			1.84 (0.81 to 4.21)	2.31 (1.04 to 5.10)
History of Coronary Stent				

Subgroup	PEGASUS			
Time to TIMI Major Bleeding	**Total N**	**Placebo N = 7,067**	**Ticagrelor 60 mg N = 7,045**	**Ticagrelor 90 mg N = 7,050**
Implantation				
Interaction term *P* value			[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo			[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo			[redacted]	[redacted]
Diabetes				
Interaction term *P* value			0.79	0.99
Yes	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.0	2.5	2.6
HR (95% CI) versus placebo			2.47 (1.40 to 4.35)	2.67 (1.52 to 4.71)
No	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.1	2.2	2.6
HR (95% CI) versus placebo			2.25 (1.52 to 3.33)	2.70 (1.84 to 3.97)
Time From Qualifying MI to Randomization				
Interaction term *P* value			0.23	0.070
< 2 years	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		1.2	2.4	2.4
HR (95% CI) versus placebo			2.05 (1.38 to 3.03)	2.18 (1.48 to 3.23)
≥ 2 years	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		0.7	2.2	2.9
HR (95% CI) versus placebo			3.17 (1.76 to 5.70)	4.15 (2.34 to 7.36)
Time Since Previous Treatment with ADP Receptor Blocker				
Interaction term *P* value			[redacted]	[redacted]
< 30 days	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo			3.37 (1.85 to 6.16)	3.44 (1.88 to 6.28)
30 days to 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo			2.92 (1.65 to 5.19)	2.86 (1.60 to 5.12)
≥ 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Kaplan–Meier % at 36 months		[redacted]	[redacted]	[redacted]
HR (95% CI) versus placebo			2.12 (1.05 to 4.25)	3.27 (1.69 to 6.32)

ADP = adenosine diphosphate; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary revascularization; TIMI = Thrombolysis in Myocardial Infarction.
Source: Clinical Study Report.[6]

TABLE 19: SUSPECTED EFFICACY EVENTS ADJUDICATED AS "NOT AN EVENT"

Outcome	PEGASUS		
	Placebo N = 6,996	**Ticagrelor 60 mg N = 6,958**	**Ticagrelor 90 mg N = 6,988**
On-Treatment Events			
Patients with downgraded suspected efficacy event, n (%)[a]	[redacted]	[redacted]	[redacted]
Any SAE, n (%)[b]	[redacted]	[redacted]	[redacted]
Any event leading to discontinuation of study drug, n (%)	[redacted]	[redacted]	[redacted]
Off-Treatment Events			
Patients with downgraded suspected efficacy event, n (%)[a]	[redacted]	[redacted]	[redacted]
Any SAE, n (%)[b]	[redacted]	[redacted]	[redacted]
Any event leading to discontinuation of study drug, n (%)	[redacted]	[redacted]	[redacted]

CDEC = CADTH Canadian Drug Expert Committee; SAE = serious adverse event; TIA = transient ischemic attack.
[a] A non-fatal event where investigator submitted a cardiac ischemic event form or a cerebrovascular event form, and the event was adjudicated by CDEC as "not a cardiac ischemic event," "not a stroke or TIA," and "not an intracranial hemorrhage."
[b] Includes fatal events.
Source: Clinical Study Report.[6]

TABLE 20: DEFINITION OF PRIMARY OUTCOMES EVENTS

Death/CV Death	MI	Stroke

"All deaths reported post-enrollment will be recorded and adjudicated.
 	
Deaths will be sub-classified by cardiovascular and non-cardiovascular primary cause.
 	
Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to a cerebrovascular event, death due to other cardiovascular causes (e.g., pulmonary embolism, aortic disease, cardiovascular intervention), and deaths for which there was no clearly documented non-cardiovascular cause (presumed CV death).
 	
Additionally, deaths will be sub-classified by coronary heart diseases death (CHD death) and non-CHD death. CHD death includes Sudden Cardiac Death, Death due to Acute MI, and the subset of Death due to other Cardiovascular Causes that are secondary to a coronary revascularization procedure."
 	
Appendix 12.1.1 Protocol, Section 6.3.1, page 41–42
	"MI is diagnosed based on the Universal MI definition (Thygesen K et al. 2007):
	– For a spontaneous MI, detection of rise and/or fall of cardiac biomarkers, preferably troponin, with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
	  – Symptoms of myocardial ischemia
	  – ECG changes (ST segment, T waves, or new left bundle branch block) indicative of new ischemia
	  – Development of pathologic Q waves on the ECG
	  – Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
	– Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
	– PCI-related MI: elevation of cardiac biomarkers > 3 x 99th percentile of the URL within 48 hours after PCI.
	– CABG-related MI: elevation of cardiac biomarkers > 5 x 99th percentile of the URL within 72 hours after CABG, plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary occlusion, or imaging evidence of loss of viable myocardium.
	– Silent MI based on ECG or imaging findings.
	– Pathological findings of an acute MI not otherwise meeting above definitions."
	
	Appendix 12.1.1 Protocol, Section 6.3.2, page 42
		"Stroke is defined as an acute episode of neurologic dysfunction attributed to a central nervous system vascular cause. Stroke should be documented by imaging (e.g., CT scan or magnetic resonance imaging [MRI] scan). Evidence obtained from autopsy can also confirm the diagnosis. Stroke will be sub-classified, when possible, as either:
		– Primary ischaemic stroke
		– Primary ischaemic stroke is defined as an acute episode of focal brain, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue and documented by imaging. A primary ischemic stroke may also undergo hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study, but appearance on a subsequent scan).
		– Primary haemorrhagic stroke
		– Primary haemorrhagic stroke is defined as an acute episode of focal or global brain, spinal, or retinal dysfunction caused by non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage as documented by neuroimaging or autopsy. Microhemorrhages (< 10 mm) evident only on MRI are not considered to be a hemorrhagic stroke. Subdural and epidural bleeding will be considered intracranial hemorrhage, but not strokes.
		
		A stroke with unknown aetiology will be classified as an unclassified stroke if the type of stroke could not be determined by imaging or other means."
		
		Appendix 12.1.1 Protocol, Section 6.3.3. page 42–43

CABG = coronary artery bypass graft; CHD = coronary heart disease; CT = computed tomography; CV = cardiovascular; ECG = electrocardiogram; LBBB = left bundle branch block; MI = myocardial infarction; MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention; URL = upper reference limit.
Source: Clinical Study Report.[6]

TABLE 21: THROMBOLYSIS IN MYOCARDIAL INFARCTION, PLATO, GUSTO, AND INTERNATIONAL SOCIETY ON THROMBOSIS AND HEMOSTASIS BLEEDING SEVERITY CLASSIFICATIONS

TIMI	PLATO	GUSTO	ISTH
TIMI major bleeding: – Any intracranial bleeding, OR – Clinically overt signs of hemorrhage associated with a drop in Hgb of ≥ 50 g/L[a] (or, when Hgb is not available, a fall in hematocrit of ≥ 15%), OR – Fatal bleeding (a bleeding event that directly led to death within 7 days).	**PLATO major bleeding** *Fatal or life-threatening* — includes bleeding events that meet any of the following criteria: – fatal bleeding – intracranial bleeding – intrapericardial bleeding with cardiac tamponade – hypovolemic shock or severe hypotension due to bleeding and requiring pressors/inotropes or surgery – decline in Hgb of 50 g/L or more (or, when Hgb is not available, a fall in hematocrit of ≥ 15%) – transfusion or 4 or more units (whole blood or PRBCs) for bleeding. *Major bleed* — other — includes bleeding events that meet any of the following criteria: – Significantly disabling (e.g., intraocular with permanent vision loss) – Clinically overt or apparent bleeding associated with a decrease in Hgb of 30 g/L to 50 g/L (or, when Hgb is not available, a fall in hematocrit of 9% to < 15%) – Transfusion of 2 to 3 units (whole blood or PRBCs) for bleeding.	**GUSTO severe bleeding** Bleeding[b] that was fatal, intracranial, or that caused hemodynamic compromise requiring intervention (e.g., systolic blood pressure < 90 mm Hg that required blood or fluid replacement, or vasopressor /inotropic support,[c] or surgical intervention).	**ISTH major bleeding** Clinically overt bleeding (including imaging) that is associated with at least one of the following: – Fatal bleeding, OR – Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular bleeding with compartment syndrome, OR – A fall in Hgb of 20 g/L or more, or a transfusion of 2 or more units of PRBCs or whole blood.

TIMI	PLATO	GUSTO	ISTH
TIMI minor bleeding Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in Hgb of 30 g/L to < 50 g/L (or, when Hgb is not available, a fall in hematocrit of 9% to < 15%).	**PLATO minor bleeding** Bleeding that: – does not meet criteria for PLATO major bleeding, AND – requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).	**GUSTO moderate bleeding** Bleeding[b] requiring transfusion of whole blood or PRBCs[d] without hemodynamic compromise (as defined above).	**ISTH minor bleeding** All non-major bleeds will be considered minor and will be divided into clinically relevant and not clinically relevant minor bleeds. Clinically relevant minor bleeds are defined as a clinically overt bleed that leads to at least one of the following: – A hospital admission for bleeding – Physician-guided medical or surgical treatment for bleeding – A change in antithrombotic therapy (including interruption of discontinuation of antithrombotic therapy).
TIMI bleeding requiring medical attention Any overt sign of hemorrhage that meets one of the following criteria and that does not meet criteria for a major or minor bleeding event, as defined above. – Requiring intervention: Defined as medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug. – Leading to hospitalization: Defined as leading to or prolonging hospitalization.	**PLATO minimal bleeding** Bleeding that: – does not meet criteria for PLATO major or minor bleeding, AND – includes all other bleeding events (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.	**GUSTO mild bleeding** Bleeding[b] without blood transfusion or hemodynamic compromise.	

TIMI	PLATO	GUSTO	ISTH
– Prompting evaluation: defined as leading to unscheduled contact with a health care professional and diagnostic testing (laboratory or imaging).			
TIMI minimal bleeding: Any overt bleeding event that does not meet the criteria above.			

CABG = coronary artery bypass graft; Hct = hematocrit; Hg = mercury; Hgb = hemoglobin; ISTH = International Society on Thrombosis and Haemostasis; PRBC = packed red blood cell; TIMI = Thrombolysis in Myocardial Infarction.

[a] To account for transfusions, Hgb measurements were adjusted for any PRBCs or whole blood given between baseline and post-transfusion measurements. A transfusion of 1 unit of blood was assumed to result in an increase by 10 g/L in Hgb. Thus, to calculate the true change in Hgb, if there has been an intervening transfusion between 2 blood measurements, the following calculations were performed:

Change in Hgb = [Baseline Hgb – post-transfusion Hgb] + [number of transfused units]; change in Hct = [Baseline Hct – post-transfusion Hct] + [number of transfused units x 3].

[b] In all cases, bleeding must be clinically overt.

[c] Need for vasopressor or inotropic support for hemodynamic compromise, even if blood pressure is > 90 mm Hg with treatment.

[d] Does not include cell-saver transfusion during CABG.

Source: Clinical Study Report.[6]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity and the minimal clinically important difference (MCID) of the EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire (EQ-5D).

TABLE 22: DETAILS OF THE EQ-5D

Instrument	Type	Evidence of Validity	MCID	References
EQ-5D	EQ-5D is a general, non–disease-specific health-related quality of life questionnaire.	Yes	CV: unknown General use: 0.033 to 0.074 for index score	Rabin 2001[11] Sinnott 2007[13]

CV = cardiovascular; EQ-5D = EuroQol 5-Dimensions Health-Related Quality of Life Questionnaire; MCID = minimal clinically important difference.

EQ-5D

The EQ-5D is a generic, non–disease-specific measure of health status.[11] The tool is based on self-report of five domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. There are three levels per domain in the original version: 1 – no problems; 2 – some or moderate problems; 3 – extreme problems. Each combination of the five domains and three levels creates a unique health-state description (243 in total). The index score is calculated by applying a country-specific, utility function–based scoring algorithm to the EQ-5D health states. This algorithm attaches weights reflecting that society's preferences for each health state.[32] An index score of 1 represents best possible health and 0 represents death, with the possibility of health states being valued as worse than death (< 0). The EQ-5D is also accompanied by a visual analogue scale (VAS) to provide a self-rating of overall health, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[11]

The EQ-5D index has been validated in a US cross-sectional study of 123 patients (mean age 64 years; 69% male; median time since last myocardial infarction [MI] 176.5 days; 89% on daily Aspirin; 64% beta blockers; 64% statins; 49% angiotensin-converting enzyme inhibitors [ACEIs]) who had experienced an MI between two and 25 months previously.[33] In addition to the EQ-5D, patients were administered the Short Form 36-Item Survey (SF-36) and McMaster Quality of Life after MI (QLMI) questionnaires. The convergent validity was determined by comparing domains of the EQ-5D with the SF-36 and QLMI using Spearman's rank correlations. The EQ-5D index was moderately correlated with the SF-36 Physical Functioning scores (0.60) and the QLMI total score (0.57). The discriminant validity was assessed by comparing differences in EQ-5D index scores between two groups based on their Canadian Cardiovascular Society Anginal Classification (CCSG) scores. The EQ-5D index showed good discrimination between patients with CCSG I versus patients with CCSG II, III, or IV ($P < 0.001$). The Spearman's correlation coefficient between the EQ-5D index and CCSG class grouping was 0.36.

The responsiveness of the EQ-5D index and VAS was assessed in a sub-study of 2,556 post-MI patients who completed the EQ-5D-5L and VAS over 24 months in the VALIANT study (N = 14,703).[34] VALIANT enrolled patients ≥ 18 years with an acute MI between 12 hours and 10 days before randomization with clinical evidence of acute heart failure. Over the study period, 597 patients experienced a non-fatal cardiovascular (CV) event. Patients who did not have a CV event experienced an improvement in their overall VAS scores during the two-year follow-up (9.6 ± 20 points) compared with patients who experienced non-fatal CV events (–8.3 ± 34 points). However, patients who experienced a CV event during follow-up had a worse overall baseline EQ-5D VAS score compared with post-MI patients who did not experience another CV event over two years (61.0 ± 19 versus 68.2 ± 18). Patients with a non-fatal CV event experienced a trajectory-adjusted mean change of –6.6 (95% CI, –8.9 to –4.3) in VAS scores after the event, suggesting a significant deterioration in their quality of life (QoL). Similar results were seen for the EQ-5D index scores.

In a German study of 106 consecutive patients with acute coronary syndrome[35] who were undergoing in-patient rehabilitation after an acute cardiac event (51% MI, 42% coronary artery bypass graft [CABG], 7% angina), the EQ-5D index and VAS were found to exhibit reasonable reliability in stable patients (intra-class correlation 0.91 to 0.54) and reasonable criterion validity when compared with the MacNew Global Score, a disease-specific instrument originally designed for measuring QoL after MI (correlation coefficient 0.63 to 0.78). The EQ-5D was found to exhibit substantial ceiling effects after rehabilitation, with 42% of patients having values in the top 10% of the EQ-5D index after three months.

Conclusion

The EQ-5D is a widely used generic health status measure consisting of five self-reported health domains with three levels per domain. The EQ-5D has demonstrated discriminant validity, convergent validity, reliability, and responsiveness in post-MI patients. The EQ-5D was found to exhibit ceiling effects in rehabilitated patients. An MCID for EQ-5D index or VAS scores in post-MI patients was not identified. The MCID for the EQ-5D index score in general use ranges from 0.033 to 0.074.[13]

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