PAR-1 Antagonists:
An Emerging Antiplatelet Drug Class
Summary

• Protease-activated receptor-1 (PAR-1) antagonists are known to be potent antiplatelet agents that are also complementary to other antiplatelet therapies. Vorapaxar and atopaxar are currently the two PAR-1 antagonist antiplatelet agents that have undergone extensive clinical development.

• Phase 3 clinical evidence is available for vorapaxar and supports its use for the reduction of thrombotic cardiovascular events in higher-risk patients with a history of myocardial infarction (MI) or peripheral artery disease (PAD). The trials examined the addition of vorapaxar to acetylsalicylic acid (ASA) and/or P2Y$_{12}$ receptor antagonists (dual and triple antiplatelet therapy) to reduce the combined end point of cardiovascular death, MI, stroke, and urgent coronary revascularization. Bleeding risk remains a concern, according to the available clinical data. In order keep a positive balance between the clinical effect and the bleeding risks, careful patient selection will be needed.

• Phase 2 clinical evidence is available for atopaxar administered in combination with ASA and/or P2Y$_{12}$ receptor antagonists. These trials reported an increased bleeding risk, although such risk seems to be limited to less severe bleeding complications. Other adverse events such as liver and cardiac toxicities may affect the future development of this drug.

• Although current available evidence limits the use of vorapaxar to a subgroup of patients with a history of MI or PAD, more clinical studies are planned for the near future; these may potentially lead to additional indications.

Background

Cardiovascular disease remains one of the most prevalent diseases in Canada, affecting 1.6 million Canadians, of whom more than 350,000 are hospitalized annually. The mortality rate associated with the condition was found to be more than 66,000 per year according to the 2011 statistics reported by the Canadian Heart and Stroke Foundation, which translates to roughly one death occurring every seven minutes. The economic burden of this disease for Canada remains high at an estimated $20.9 billion annually in physician services, hospital costs, lost wages, and decreased productivity.
Because there are multiple signaling pathways involved in platelet aggregation, multiple antiplatelet drug classes currently exist to reduce platelet activity.\(^7\)

Ischemic heart disease (IHD; otherwise known as coronary artery disease, or CAD) is a type of cardiovascular disease that accounts for a large portion of the morbidity and mortality associated with cardiovascular disease.\(^2\) This condition is characterized by the narrowing of the blood vessels that supply oxygen and nutrients to the heart. More than 90% of myocardial infarctions (MIs), also known as heart attacks, are a direct result of the progression of atherosclerosis.\(^3\) Atherosclerosis is the narrowing of coronary arteries caused by plaque building up on the artery wall that slowly obstructs blood flow. Plaque builds up over many years and consists of a sticky, fat-like substance of which cholesterol is one of the components, along with other waste products from cells in the body. Sometimes the fibrous cap of a plaque can rupture, releasing thrombogenic material promoting platelet aggregation and thrombus formation. The latter may result in the progressive occlusion (blockage) of the vessel leading to cardiac ischemia when the occlusion is advanced. The thrombus can also detach from the vessel wall (blood clot) and block a smaller blood vessel downstream, causing an MI (in the heart) or a stroke (in the brain). Also related to atherosclerosis, peripheral artery disease (PAD) occurs when plaques accumulate in the blood vessels of the lower extremities (e.g., the legs), resulting in poor peripheral circulation, pain, and difficulty walking. One of the mainstays of therapy in preventing or reducing thrombosis in the event of plaque rupture involves using antiplatelet drugs to prevent platelet aggregation — the early stage of the blood-clotting process.\(^4,6\)

The Technology

Because there are multiple signaling pathways involved in platelet aggregation, multiple antiplatelet drug classes currently exist to reduce platelet activity.\(^7\) These classes include thromboxane A2 synthesis/cyclooxygenase inhibitors (such as acetylsalicylic acid [ASA]), phosphodiesterase inhibitors (such as dipyridamole), glycoprotein IIb/IIIa antagonists (such as abciximab), and the P2Y\(^{12}\) receptor antagonists (such as clopidogrel).\(^7\) ASA and P2Y\(^{12}\) receptor antagonists are widely used in clinical practice, both in the acute treatment of MI (such as acute coronary syndrome [ACS]), as well as in the secondary prevention of future MIs.\(^8\) The combination of ASA and a P2Y\(^{12}\) receptor antagonist is often prescribed as dual antiplatelet therapy (DAPT) following non–ST elevation myocardial infarction (NSTEMI), a type of MI, to reduce the chance of future MIs.\(^9\)

Despite the widespread use of clopidogrel as a P2Y\(^{12}\) receptor antagonist, some patients may not fully respond to it (largely as a result of genetic variability among patients) and so other P2Y\(^{12}\) receptor antagonists such as prasugrel and ticagrelor have been developed.\(^7\) A 2012 systematic review that examined the prevalence of patients resistant to clopidogrel found that between 16% and 50% could be non-responders.\(^10\) Genotypic testing to identify antiplatelet resistance has been suggested as a potential solution, although the impact of such testing on cardiovascular events is still uncertain.\(^11\) Overall, despite the availability of DAPT as a standard of care, there is still high morbidity and mortality associated with ACS and recurrent thrombotic events in CAD.\(^12,13\)

Recently, a new antiplatelet drug class has emerged; it is called protease-activated receptor-1 (PAR-1) antagonists. This new drug class exerts its pharmacologic effect through a separate signalling pathway that is complementary to those inhibited by ASA and the P2Y\(^{12}\) receptor antagonists.\(^7\) PAR-1 antagonists, also known as thrombin-receptor antagonists, prevent the cleavage of the extracellular domain of the PAR-1 receptor by thrombin, without inhibiting other functions of thrombin (such as the coagulation cascade).\(^7\) The thrombin pathway of platelet activation has been of particular interest because it has been found to be more potent compared with pathways inhibited by ASA or P2Y\(^{12}\) receptor antagonists — that is, thromboxane A2 synthesis and adenosine diphosphate (ADP)-mediated signalling, respectively.\(^7\) Preliminary studies of PAR-1 antagonists found acceptable bleeding risks; also, these drugs can be administered orally to patients on a daily basis.\(^7\) Because of the complementary nature of PAR-1 antagonists to ASA and P2Y\(^{12}\) receptor antagonists, questions have been raised about whether there may be a role in evolving DAPT to triple antiplatelet therapy.\(^14\) Currently, there are two PAR-1 antagonists with clinical trial data available (Table 1): vorapaxar...
### Table 1: PAR-1 Antagonists Currently Being Developed

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Metabolism</th>
<th>Half-Life</th>
<th>Route of Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorapaxar (SCH 530348)</td>
<td>Oral</td>
<td>Mainly CYP3A4</td>
<td>159 to 311 hours</td>
<td>Primarily feces</td>
</tr>
<tr>
<td>Atopaxar (E5555)</td>
<td>Oral</td>
<td>Mainly CYP3A4</td>
<td>~23 hours</td>
<td>Primarily feces</td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; PAR-1 = protease-activated receptor-1.

### Figure 1: Mechanisms of Action of Antiplatelet Drugs

Source: Reprinted from Franchi et al. 2015, with permission from Nature Publishing Group.

Note: Some of the drugs presented in Figure 1 are not commercially available in Canada.
(SCH 530348) and atopaxar (E5555). Figure 1 depicts how PAR-1 antagonists work, along with the mechanism of actions of drugs belonging to the other antiplatelet classes.

**Regulatory Status**

With regard to vorapaxar, phase 3 clinical trial data has been available since 2012, and the parent drug company Merck has filed for submission of approval to the US FDA, as well as the European Medicines Agency (EMA). The FDA issued approval of vorapaxar on May 8, 2014 and the EMA followed with their approval on January 19, 2015. Merck is currently in the process of filing for regulatory approval with Health Canada; the date at which a decision will be made by Health Canada is currently unknown (Shelley Epstein, Director, Access Planning, Merck Canada Inc., Kirkland, QC: personal communication, 2016 Feb 2). At this time, Eisai Limited (the parent company of atopaxar) does not plan to seek market authorization for atopaxar in Canada (Laveena Kamboj, Director, Market Access & Government Affairs, Eisai Limited, Mississauga, ON: personal communication, 2016 Feb 1). Of note, the clinical development of atopaxar is currently limited to phase 1 and 2 trials.

**Patient Group**

Originally, there were two distinct groups of patients anticipated to benefit from treatment with a PAR-1 antagonist — the first group being older adults with typically at least one higher cardiovascular risk (e.g., diabetes) presenting to the emergency department with a recent onset of ACS symptoms; and the second group being patients with established atherosclerosis who have had a recent (i.e., within the past two to 52 weeks) cardiovascular event such as an MI or stroke, or have PAD with claudication, and who would benefit from the prevention of a future atherosclerotic event. These patients generally tend to have greater disease burden (i.e., more comorbidities) compared with ACS patients because of their established history of blood vessel narrowing. In 2005-2006, it was reported that approximately 160,000 hospitalizations per year in Canada were due to IHD, and 60,000 annual hospitalizations were due to MIs alone. In 2004, the number of deaths related to these conditions were close to 40,000 and 18,000, respectively. Atherosclerosis can also manifest as PAD, leading to the inability to walk because of constant pain. Whereas intermittent claudication — or pain in the leg muscles with ambulation — is the most common symptom, in later stages of the disease, tissue hypoperfusion may lead to limb ischemia, a complication associated with increased mortality. The longevity of patients with PAD may also be reduced from atherosclerotic complications in the coronary and cerebrovascular beds.

Vorapaxar was recently approved in two key jurisdictions: the FDA approved the drug for the reduction of thrombotic cardiovascular events in patients with a history of MI or with PAD, and EMA approved it for the reduction of thrombotic cardiovascular events in those with a history of MI. (Note: The EMA did not approve vorapaxar for PAD because that indication was not included in the original filing [Shelley Epstein: personal communication, 2016 Feb 2]). Of note, vorapaxar is not approved in these jurisdictions for treating patients presenting to the hospital with symptoms of ACS, in countries where it has been approved, the place in therapy of vorapaxar is as an add-on drug to ASA, with or without clopidogrel. Use in combination with other antiplatelet agents (e.g., another thienopyridine or dipyridamole) is not well-established. Vorapaxar has not been studied for use as monotherapy and, in countries where the drug is available, it is contraindicated in patients with a history of stroke, transient ischemic attack (TIA), intracranial hemorrhages, or active bleeding such as peptic ulcers.

**Current Practice**

For patients presenting to the hospital with NSTEMI ACS, and being considered for percutaneous coronary intervention (PCI), the current standard of care for antiplatelet therapy is DAPT, involving the administration of 162 mg to 325 mg of ASA at initial presentation plus a P2Y₁₂ receptor antagonist (e.g., 300 mg to 600 mg of clopidogrel, 60 mg of prasugrel, or 180 mg of ticagrelor) as the loading dose. Alternatively, when angiography determines that there is a need to increase coronary vessel patency but stent insertion is deemed unsuitable, the patient will undergo a coronary artery bypass graft (CABG) surgery to restore blood flow to the heart. PCI patients will remain on a maintenance dose of 81 mg ASA daily, together with a P2Y₁₂ receptor antagonist (i.e., either clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily) for up to 12 months (shorter DAPT duration in
patients at increased bleeding risk after stent implantation,\(^8\) sometimes longer duration can be considered in patients at a higher risk of recurrence of cardiovascular events and lower bleeding risks\(^7\). The maintenance phase of DAPT would be considered as secondary prevention of future MI because the patient will have already established a history of CAD.\(^8\) Of note, recent evidence showed cardiovascular benefits (reduction in the rate of composite end point [cardiovascular death, MI, or stroke]) with long-term (three years; median time = 33 months) secondary prevention with DAPT (low-doses ASA + ticagrelor), compared with ASA monotherapy, in stable patients with a history of spontaneous MI (one to three years prior to study enrolment; median time = 1.7 years). These patients also had at least one high-risk condition (e.g., diabetes requiring medication or multivessel CAD). The reported cardiovascular benefit was, however, associated with an increase in Thrombolysis in Myocardial Infarction (TIMI)-defined major bleeding.\(^28\)

Table 2: Phase 2 or 3 Clinical Trial Designs for PAR-1 Antagonists\(^{12,13,29-31}\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Study Design/Intervention/Comparator/Duration</th>
<th>Primary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vorapaxar TRACER Phase 3</td>
<td>To determine whether the addition of vorapaxar to standard therapy would be superior to placebo in reducing recurrent ischemic cardiovascular events and to determine its safety profile in patients with NSTEMI ACS.</td>
<td>Design: Multinational, randomized, double-blind, placebo-controlled. Intervention: loading dose of 40 mg followed by 2.5 mg vorapaxar daily for minimum of 1 year. Comparator: Placebo with same dosing as above-mentioned. Of note, during the trial, investigators were encouraged to follow current practice guidelines.</td>
<td>Efficacy: Composite of death from cardiovascular causes, MI, stroke, recurrent ischemia with re-hospitalization, or urgent coronary revascularization (primary), and composite of death from cardiovascular causes, MI, or stroke (secondary). Safety: Composite of moderate or severe bleeding according to GUSTO classification and clinically significant bleeding according to TIMI classification.</td>
</tr>
<tr>
<td>Vorapaxar TRA 2P-TIMI 50 Phase 3</td>
<td>To evaluate the efficacy and safety of adding vorapaxar to standard therapy in reducing atherothrombotic events in patients with established history of MI, ischemic stroke, or PAD.</td>
<td>Design: Multinational, randomized, double-blind, placebo-controlled. Intervention: 2.5 mg vorapaxar given daily until end of follow-up (median of 30 months) in addition to standard of care. Comparator: Matched placebo in addition to standard of care.</td>
<td>Efficacy: Composite of cardiovascular death, MI, and stroke (primary), and composite of cardiovascular death, MI, stroke, or urgent coronary revascularization (secondary). Safety: Moderate or severe bleeding according to the GUSTO classification (primary) and clinically significant bleeding according to TIMI classification.</td>
</tr>
<tr>
<td>Study</td>
<td>Purpose</td>
<td>Study Design/Intervention/Comparator/Duration</td>
<td>Primary Outcomes</td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>---------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Atopaxar LANCELOT-ACS Phase 2 N = 603</td>
<td>To examine the safety and tolerability of atopaxar in patients with ACS.</td>
<td>Design: Multinational, randomized, double-blind, placebo-controlled. Intervention: Atopaxar 400 mg loading dose followed by: • Atopaxar 50 mg q.d. • Atopaxar 100 mg q.d. • Atopaxar 200 mg q.d. Comparator: Placebo. Duration: 12 weeks. Of note, during the trial, investigators were encouraged to follow current practice guidelines.</td>
<td>Safety: Major and minor bleeding according to CURE bleeding classification. Clinically significant bleeding according to TIMI classification (major, minor, minimal).</td>
</tr>
<tr>
<td>Atopaxar J-LANCELOT-ACS Phase 2 N = 241</td>
<td>To evaluate the safety and tolerability of atopaxar in Japanese patients with ACS.</td>
<td>Design: Multicentred, randomized, double-blind, placebo-controlled. Intervention: Atopaxar 400 mg loading dose followed by: • Atopaxar 50 mg q.d. • Atopaxar 100 mg q.d. • Atopaxar 200 mg q.d. Comparator: Placebo. Duration: 12 weeks.</td>
<td>Safety: Major and minor bleeding according to CURE bleeding classification. Clinically significant bleeding according to TIMI classification (major, minor, minimal).</td>
</tr>
<tr>
<td>Atopaxar LANCELOT-CAD Phase 2 N = 720</td>
<td>To examine the safety and tolerability of atopaxar in patients with CAD.</td>
<td>Design: Multinational, randomized, double-blind, placebo-controlled. Intervention: • Atopaxar 50 mg q.d. • Atopaxar 100 mg q.d. • Atopaxar 200 mg q.d. Comparator: Placebo Duration: 24 weeks</td>
<td>Safety: Major and minor bleeding according to CURE bleeding classification. Clinically significant bleeding according to TIMI classification (major, minor, minimal).</td>
</tr>
</tbody>
</table>
The Evidence

Available evidence on PAR-1 antagonists comes from two large phase 3 studies for vorapaxar and four phase 2 studies for atopaxar. These six trials are summarized in Table 2.

**Vorapaxar**

The first phase 3 study of vorapaxar was the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial. This trial focused on patients with ACS by looking at the safety and efficacy of vorapaxar following their presentation to the hospital with NSTEMI. Patients were randomized into two groups at a 1:1 ratio — a treatment group that received 40 mg of vorapaxar as a loading dose (at least one hour before any coronary revascularization procedure) and was maintained on 2.5 mg of vorapaxar daily for the remainder of the study (minimum one year), and a control group that received a placebo. Patients in both groups were also stratified depending on the investigator’s decision to concurrently use a glycoprotein IIb/IIia inhibitor and/or a direct thrombin inhibitor. Although the control group received a placebo, investigators were encouraged to follow standard-of-care practice guidelines pertaining to ACS; therefore, the majority of patients in the trial (both treatment and control groups) were anticipated to be on a combination of ASA and a P2Y₁₂ receptor antagonist.

The primary safety end point of this study was a composite of death from cardiovascular causes, MI, stroke, recurrent ischemia with re-hospitalization, or urgent coronary revascularization. The main safety end points of this study were a composite of moderate or severe bleeding according to the Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO) classification and clinically significant bleeding (major, minor, or requiring unplanned treatment or testing) according to the TIMI classification.

ACS = acute coronary syndrome; CAD = coronary artery disease; CURE = Clopidogrel in Unstable angina to prevent Recurrent Events trial; GUSTO = Global Use of Strategies To Open Occluded Coronary Arteries trial; LANCELOT = Lesson from Antagonizing the Cellular Effect of Thrombin trial; MI = myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; PAD = peripheral artery disease; PAR-1 = protease-activated receptor-1; q.d. = once daily; TIMI = Thrombolysis in Myocardial Infarction trial risk score; TRACER = Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome study; TRA 2P-TIMI 50 = Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events – Thrombolysis in Myocardial Infarction 50 trial.

### Table 2: Phase 2 or 3 Clinical Trial Designs for PAR-1 Antagonists

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Study Design/Intervention/Comparator/Duration</th>
<th>Primary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopaxar</td>
<td>To evaluate the safety and tolerability of atopaxar in Japanese patients with CAD.</td>
<td>Design: Multicentred, randomized, double-blind, placebo-controlled.</td>
<td>Safety: Major and minor bleeding according to CURE bleeding classification.</td>
</tr>
<tr>
<td>J-LANCELOT-CAD</td>
<td></td>
<td>Intervention:</td>
<td>Clinically significant bleeding according to TIMI classification (major, minor, minimal).</td>
</tr>
<tr>
<td>Phase 2</td>
<td></td>
<td>• Atopaxar 50 mg q.d.</td>
<td></td>
</tr>
<tr>
<td>N = 263</td>
<td></td>
<td>• Atopaxar 100 mg q.d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Atopaxar 200 mg q.d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparator: Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration: 24 weeks</td>
<td></td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; CAD = coronary artery disease; CURE = Clopidogrel in Unstable angina to prevent Recurrent Events trial; GUSTO = Global Use of Strategies To Open Occluded Coronary Arteries trial; LANCELOT = Lesson from Antagonizing the Cellular Effect of Thrombin trial; MI = myocardial infarction; NSTEMI = non–ST elevation myocardial infarction; PAD = peripheral artery disease; PAR-1 = protease-activated receptor-1; q.d. = once daily; TIMI = Thrombolysis in Myocardial Infarction trial risk score; TRACER = Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome study; TRA 2P-TIMI 50 = Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events – Thrombolysis in Myocardial Infarction 50 trial.
Patients enrolled in the study were between 53 and 78 years of age (interquartile range), with a high prevalence of hyperlipidemia (approximately 83%), CAD (approximately 78%), and hypertension (approximately 69%). Approximately two-thirds of the patients were enrolled in the MI subgroup, with 18% and 14% enrolled in the stroke and PAD subgroups, respectively.

Antiplatelet use was highest among patients in the MI subgroup, with 98% being on ASA and approximately two-thirds of the patients were enrolled in the MI subgroup, with 98% being on ASA and approximately 78% on P2Y$_{12}$ receptor antagonists; and it was lowest in the PAD subgroup, with about 81% being on ASA and roughly 24% being on P2Y$_{12}$ receptor antagonists.

After a median follow-up duration of 24 months, the data and safety monitoring board recommended the discontinuation of vorapaxar in all patients with previous strokes, including patients with a new stroke. The board also recommended continuation of the trial in patients without a history of stroke. The study protocol was amended to meet these recommendations.

The primary efficacy end point was met after three years of follow-up, with a 9.3% composite event rate in the treatment group compared with 16.2% in the vorapaxar group and 15.1% in the placebo group (HR: 0.89; 95% CI: 0.81 to 0.98; $P = 0.02$).

In terms of safety outcomes, vorapaxar increased the rate of GUSTO moderate or severe bleeding with respect to placebo (7.2% versus 5.2%; HR: 1.35; 95% CI: 1.16 to 1.58; $P < 0.001$).

The rate of clinically significant TIMI bleeding was also increased in the vorapaxar group (20.2% versus 14.6%; HR: 1.43; 95% CI: 1.31 to 1.57; $P < 0.001$).

For the comparison of vorapaxar versus placebo, the HR for hemorrhagic stroke was 2.73 (95% CI: 1.22 to 6.14; $P = 0.02$) and the HR for intracranial hemorrhage was 3.39 (95% CI: 1.78 to 6.45; $P < 0.001$).

The investigators also commented on a subgroup analysis of patients taking vorapaxor without P2Y$_{12}$ inhibitors who had more pronounced efficacy without increased bleeding; further studies are required to determine if intracranial bleeding was a result of an intensive antiplatelet strategy or specific to PAR-1 inhibition, only. Overall, this clinical trial was deemed unsuccessful because of primary end points not being met and the increase in bleeding risk.

The second phase 3 study was the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events – Thrombolysis in Myocardial Infarction 50 (TRA 2P-TIMI 50) trial.

This trial focused on the safety and efficacy of vorapaxor in patients with a history of atherosclerotic disease and was conducted parallel to the TRACER study. In the TRA 2P-TIMI 50 trial, atherosclerosis was defined as a spontaneous MI or ischemic stroke within the previous two weeks to 12 months or PAD associated with a history of intermittent claudication in conjunction with either an ankle-brachial index of less than 0.85 or previous revascularization for limb ischemia.

Individuals in both treatment and control (placebo) groups were enrolled into three subgroups (MI, stroke, and PAD).

Patients were randomized into two groups at a 1:1 ratio — a treatment group receiving 2.5 mg of vorapaxor daily and a control group receiving placebo until the end of follow-up (median duration was 30 months).

Investigators were also encouraged to follow the current standard of care (e.g., use of other antiplatelet agents) as they carried out this clinical trial. The primary efficacy end point of this study was a composite of cardiovascular death, MI, or stroke.

In the TRA 2P-TIMI 50 trial, investigators used GUSTO (primary) and TIMI (secondary) classifications to evaluate safety end points. Baseline demographic characteristics between the treatment and control groups were comparable, with no statistically significant differences other than the renal function, which was lower in the vorapaxor group (i.e., the rate of estimated glomerular filtration rate < 60 mL/min was 16.2% in the vorapaxor group and 15.1% in the placebo group; $P < 0.05$).

Patients enrolled in the study were between 53 and 69 years of age (interquartile range), with a high prevalence of hyperlipidemia (approximately 83%), CAD (approximately 78%), and hypertension (approximately 69%).

Approximately two-thirds of the patients were enrolled in the MI subgroup, with 18% and 14% enrolled in the stroke and PAD subgroups, respectively.

Antiplatelet use was highest among patients in the MI subgroup, with 98% being on ASA and approximately 78% on P2Y$_{12}$ receptor antagonists; and it was lowest in the stroke subgroup, with about 81% being on ASA and roughly 24% being on P2Y$_{12}$ receptor antagonists.

After a median follow-up duration of 24 months, the data and safety monitoring board reported an excess of intracranial bleeding among patients with a history of stroke (including the development of new strokes during the trial) in the vorapaxor group. As a result, the board recommended the discontinuation of vorapaxar in all patients with previous strokes, including patients with a new stroke. The board also recommended continuation of the trial in patients without a history of stroke. The study protocol was amended to meet these recommendations.

The primary efficacy end point was met after three years of follow-up, with a 9.3% composite event rate in the treatment group compared with 16.2% in the vorapaxor group and 15.1% in the placebo group (HR: 0.89; 95% CI: 0.81 to 0.98; $P = 0.02$).

In terms of safety outcomes, vorapaxor increased the rate of GUSTO moderate or severe bleeding with respect to placebo (7.2% versus 5.2%; HR: 1.35; 95% CI: 1.16 to 1.58; $P < 0.001$).

The rate of clinically significant TIMI bleeding was also increased in the vorapaxor group (20.2% versus 14.6%; HR: 1.43; 95% CI: 1.31 to 1.57; $P < 0.001$).

For the comparison of vorapaxor versus placebo, the HR for hemorrhagic stroke was 2.73 (95% CI: 1.22 to 6.14; $P = 0.02$) and the HR for intracranial hemorrhage was 3.39 (95% CI: 1.78 to 6.45; $P < 0.001$).

The investigators also commented on a subgroup analysis of patients taking vorapaxor without P2Y$_{12}$ inhibitors who had more pronounced efficacy without increased bleeding; further studies are required to determine if intracranial bleeding was a result of an intensive antiplatelet strategy or specific to PAR-1 inhibition, only. Overall, this clinical trial was deemed unsuccessful because of primary end points not being met and the increase in bleeding risk.

The second phase 3 study was the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events – Thrombolysis in Myocardial Infarction 50 (TRA 2P-TIMI 50) trial. This trial focused on the safety and efficacy of vorapaxor in patients with a history of atherosclerotic disease and was conducted parallel to the TRACER study. In the TRA 2P-TIMI 50 trial, atherosclerosis was defined as a spontaneous MI or ischemic stroke within the previous two weeks to 12 months or PAD associated with a history of intermittent claudication in conjunction with either an ankle-brachial index of less than 0.85 or previous revascularization for limb ischemia.

Individuals in both treatment and control (placebo) groups were enrolled into three subgroups (MI, stroke, and PAD). Patients were randomized into two groups at a 1:1 ratio — a treatment group receiving 2.5 mg of vorapaxor daily and a control group receiving placebo until the end of follow-up (median duration was 30 months).

Investigators were also encouraged to follow the current standard of care (e.g., use of other antiplatelet agents) as they carried out this clinical trial. The primary efficacy end point of this study was a composite of cardiovascular death, MI, or stroke. In the TRA 2P-TIMI 50 trial, investigators used GUSTO (primary) and TIMI (secondary) classifications to evaluate safety end points. Baseline demographic characteristics between the treatment and control groups were comparable, with no statistically significant differences other than the renal function, which was lower in the vorapaxor group (i.e., the rate of estimated glomerular filtration rate < 60 mL/min was 16.2% in the vorapaxor group and 15.1% in the placebo group; $P < 0.05$).

Patients enrolled in the study were between 53 and 69 years of age (interquartile range), with a high prevalence of hyperlipidemia (approximately 83%), CAD (approximately 78%), and hypertension (approximately 69%).

Approximately two-thirds of the patients were enrolled in the MI subgroup, with 18% and 14% enrolled in the stroke and PAD subgroups, respectively. Antiplatelet use was highest among patients in the MI subgroup, with 98% being on ASA and approximately 78% on P2Y$_{12}$ receptor antagonists; and it was lowest in the stroke subgroup, with about 81% being on ASA and roughly 24% being on P2Y$_{12}$ receptor antagonists.

After a median follow-up duration of 24 months, the data and safety monitoring board reported an excess of intracranial bleeding among patients with a history of stroke (including the development of new strokes during the trial) in the vorapaxor group. As a result, the board recommended the discontinuation of vorapaxor in all patients with previous strokes, including patients with a new stroke. The board also recommended continuation of the trial in patients without a history of stroke. The study protocol was amended to meet these recommendations.
To reflect the balance between cardiovascular benefits and bleeding risks, authors of the TRA 2P-TIMI 50 study developed a (pre-specified) composite end point called “net clinical outcome.” This end point incorporated the efficacy and safety end points. The composite of cardiovascular death, MI, stroke, or GUSTO moderate or severe bleeding suggests a net benefit of vorapaxar over placebo, with rates of events of 11.7% for vorapaxar compared with 12.1% for placebo (HR = 0.97; 95% CI, 0.90 to 1.04; P = 0.40). It is important to note that the overall safety and efficacy analysis included patients in the stroke subgroup whose participation was ended early. To further investigate the cardiovascular benefits/bleeding risks ratio of vorapaxar, a number of subgroup analyses were conducted based on findings from the TRA 2P-TIMI 50 trial that were specific to patients with no history of stroke or TIA; some of these are described, as follows:

- In patients with a previous MI and with diabetes, vorapaxar (11.4%) statistically significantly reduced the primary end point compared with placebo (14.3%) (HR = 0.73, 95% CI, 0.60 to 0.89; P = 0.002). The risk of moderate to severe bleeding was increased with vorapaxar (4.4%) compared with placebo (2.6%) (HR = 1.60, 95% CI, 1.07 to 2.40). The net clinical outcome was improved with vorapaxar (HR = 0.79, 95% CI, 0.67 to 0.93).

- In an analysis to determine whether the efficacy and safety of vorapaxar was modified by the concurrent use of the P2Y12 receptor antagonist, it was found that, compared with placebo, vorapaxar significantly reduced the composite of cardiovascular death, MI, and stroke regardless of planned P2Y12 receptor antagonist therapy (planned P2Y12 receptor antagonist, HR = 0.80, 95% CI, 0.70 to 0.91; P < 0.001; and no planned P2Y12 receptor antagonist, HR = 0.75, 95% CI, 0.60 to 0.94; P = 0.011). GUSTO moderate or severe bleeding was increased with vorapaxar and was not statistically significantly modified by the use of the P2Y12 receptor antagonist (planned P2Y12 receptor antagonist, HR = 1.50; 95% CI, 1.18 to 1.89; P < 0.001; and no planned P2Y12 receptor antagonist, HR = 1.90, 95% CI, 1.17 to 3.07; P = 0.009).

- In patients with PAD, vorapaxar (2%) significantly reduced the risk of hospitalization for acute limb ischemia—a serious complication of PAD—compared with placebo (3.3%) (HR = 0.59, 95% CI, 0.40 to 0.86; P = 0.007). On the other hand, the risk of moderate to severe GUSTO bleeding was increased with vorapaxar (6.6%) versus placebo (4.5%) (HR = 1.50, 95% CI, 1.14 to 1.98; P = 0.003).

- In patients with severe CAD previously treated with CABG, vorapaxar statistically significantly reduced the risk of cardiovascular death, MI, or stroke (11.9%), compared with placebo (15.6%), (HR = 0.71, 95% CI, 0.58 to 0.88; P = 0.001). In patients on vorapaxar while undergoing CABG, the risk of TIMI CABG major bleeding was 6.3%, versus 4.1% with placebo (HR = 1.53, 95% CI, 0.58 to 4.01; P = 0.39).

- In an analysis of outcomes associated with new ischemic stroke, vorapaxar was found to reduce the risk of first ischemic stroke (HR = 0.87, 95% CI, 0.43 to 0.75; P < 0.001). Compared with placebo, the risk of hemorrhagic conversion after stroke was not significantly increased (HR: 1.19, 95% CI: 1.00 to 7.73; P = 0.049). Authors calculated that the overall stroke risk was significantly reduced in this population (HR: 0.67, 95% CI: 0.52 to 0.87; P = 0.002) with vorapaxar versus placebo.

Although some of the subgroup analyses performed were pre-specified, a number of limitations (e.g., the small number of patients in some subgroups) are associated with such analyses and, therefore, interpretation of these findings should be done with caution. All in all, the TRA 2P-TIMI 50 trial demonstrated a reduced risk of cardiovascular death, MI, or stroke among patients with stable atherosclerosis when vorapaxar was added on to standard therapy. Of note, the latter often involved the combined use of ASA and a P2Y12 receptor antagonist, mostly clopidogrel. The trial also reinforced the fact that vorapaxar increases the risks of moderate or severe bleeding, including intracranial hemorrhages; this was particularly pronounced in patients with a prior history of stroke. As such, careful assessment of bleeding risks will be crucial in selecting patients for intensive antiplatelet therapy with vorapaxar. As suggested by the result of the previously mentioned subgroup analyses,
given part of the cardiovascular benefits of vorapaxar may be offset by significant increased bleeding risks, there seems to be substantial effort currently deployed in determining the subpopulations that may benefit most from this therapy.

Of interest, using data from patients with previous MI without stroke or TIA enrolled in the TRA 2P-TIMI 50 trial, a risk stratification strategy was recently proposed to guide patient selection for secondary prevention intensive antiplatelet therapy with vorapaxar. After identifying nine independent risk predictors (age, diabetes, hypertension, smoking, PAD, previous stroke, previous CABG, heart failure, and renal dysfunction), three risk categories were defined: low-risk (zero risk predictors), intermediate-risk (one to two risk predictors), and high-risk (three or more risk predictors). Accounting for the cardiovascular benefits (composite of cardiovascular death, MI, and stroke), as well as bleeding complications (GUSTO severe bleeding), the net clinical outcome was in favour of vorapaxar use in the intermediate- and high-risk categories, with absolute risk reductions of 2.0% (95% CI: 0.7 to 3.3) and 3.5% (95% CI: 0.4 to 6.6), respectively. For the low-risk category, the net clinical outcome was not in favour of vorapaxar versus placebo, with absolute risk difference of −0.4% (95% CI, −2.1 to 1.3). Based on these findings, and acknowledging the limitations of the risk stratification tool developed, it would appear that intensive antiplatelet secondary preventive therapy involving vorapaxar would be considered mainly in higher-risk patients. These are stable IHD patients with previous MI but no stroke; it may be added that they also have a lower bleeding risk.

**Atopaxar**

The majority of the evidence on atopaxar came from the Lesson from Antagonizing the Cellular Effect of Thrombin (LANCELOT) phase 2 trials, which had two target populations (i.e., ACS and CAD). Patients with ACS were enrolled in LANCELOT-ACS and J-LANCELOT-ACS, which were similarly designed but had different ethnic groups (LANCELOT-ACS being an international trial whereas J-LANCELOT-ACS included only a Japanese population). The goals of these two studies were to look at the safety and tolerability of atopaxar in patients with ACS. These two trials were also dose-ranging studies to determine an optimal dose to minimize harm while preserving efficacy of atopaxar. Patients were randomized into four groups at a 1:1:1:1 ratio — three treatment groups (400 mg loading dose followed by either a 50 mg, 100 mg, or 200 mg maintenance dose daily) and a control group that received a placebo following enrolment into the studies. Investigators were also encouraged to follow current standard-of-care guidelines for ACS (e.g., use of beta-blockers, antiplatelet drugs, etc.) regardless of whether a patient was in a treatment group or the control group. The studies were planned for 12 weeks in total and included in-patients admitted with NSTEMI or unstable angina with new onset/worsening ischemic symptoms either at rest or with minimal activity. The primary point of these two studies was the proportion of patients with major bleeding according to the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) bleeding classification (defined as significantly disabling bleeding, bleeding requiring two units or more of red blood cells or equivalent, intracranial or intraocular hemorrhage, bleeding requiring inotropes or surgical intervention, or bleeding leading to death). Bleeding was also classified according to the TIMI bleeding definition (major, minor, and minimal, with minimal defined as overt bleeding that does not meet the major or minor category). The mean age of patients in the LANCELOT-ACS and J-LANCELOT-ACS trials ranged between 62 to 65 years, depending on the randomized groups. The proportion of patients on background ASA therapy was high and similar between the study groups and between the trials (95% and 100%). P2Y12 receptor antagonist use was higher in the Japanese study (93% to 95%) compared with the international study (80% and 84%).

The results of the smaller Japanese study (n = 241) showed no increases in any CURE bleeding between the combined (50 mg, 100 mg, 200 mg) atopaxar group and the control group (0.6% versus 3.3%; P = 0.125); there was also no statistically significant difference in the rate of TIMI bleeding in the combined atopaxar group versus the control group (19.4% versus 16.4%; P = 0.61). In the larger international trial (n = 603), there was no statistically significant difference in major and minor CURE bleeding between the placebo and the combined atopaxar groups (2.2% versus 3.1%; I = 0.63). There was also no statistically significant difference in TIMI bleeding (any type) between the control group and the combined atopaxar group (10.1% versus 9.2%; P = 0.77). There was no dose-dependent increase in risk in either the TIMI or CURE bleeding risks among the 50 mg, 100 mg, and 200 mg atopaxar groups (TIMI: P = 0.63; CURE: P = 0.80). There was no statistically significant difference between the combined atopaxar and control groups (8% versus 7.8%,
respectively; \( P = 0.93 \) in the composite of cardiovascular death, MI, stroke, or recurrent ischemia. Although a numerical decrease was observed in favour of atopaxar, there was no statistically significant difference between the combined atopaxar and control groups in the rate of cardiovascular death, MI, or stroke (i.e., 3.3\% versus 5.6\%; \( P = 0.20 \)).\(^{29}\) Continuous electrocardiogram monitoring was performed in 561 patients in the LANCELOT-ACS trial. It reported a 34\% reduction in Holter-detected ischemia during the first 48 hours after the 400 mg atopaxar loading dose in the combined atopaxar treatment group, compared with the control group (relative risk [RR]: 0.67; 95\% CI: 0.48 to 0.94; \( P = 0.02 \)).\(^{29}\) Of note, interpretation of efficacy outcomes should be done cautiously, as the LANCELOT-ACS trial was not powered to assess clinical efficacy.

In the international study, an increase in alanine aminotransferase levels (≥3 times upper limit of normal) was observed more frequently after two weeks of therapy with atopaxar 200 mg, compared with placebo (5.5\% versus 2.5\%).\(^{29}\) Regarding other adverse events, a relative QTc prolongation was observed more frequently with atopaxar (mainly the 100 mg and 200 mg doses) versus placebo. This was measured as a greater mean decrease in QTcF (Fridericia’s formula) in the placebo group than in the combined atopaxar group (−11.4 milliseconds versus −6.4 milliseconds; \( P = 0.04 \)), after the ACS event (i.e., QTc intervals were prolonged during ACS but shortened less in the combined atopaxar group compared with the control group).\(^{29}\) The smaller Japanese study also showed a similar dose-dependent increase in liver enzymes, as well as QTc prolongations.\(^{31}\)

With regard to the CAD population, enrolment in LANCELOT-CAD and J-LANCELOT-CAD allowed atopaxar to be studied over a longer term (24 weeks) and looked at the safety and tolerability at various doses (50 mg to 200 mg).\(^{30,31}\) The respective design of these trials was very similar, with a larger international trial (LANCELOT-CAD; \( n = 720 \)) and a smaller Japanese trial (J-LANCELOT-CAD; \( n = 263 \)).\(^{30,31}\) The studies enrolled patients with a history of high-risk CAD defined as: i) previous ACS (including MI or unstable angina) at least four weeks previously, ii) percutaneous coronary revascularization at least 12 weeks previously, and iii) angina with documented ischemia by provocative testing or angiographically evident CAD (>70\%) and at least one high-risk indicator (high-sensitivity C-reactive protein >3.0 mg/L, diabetes, PAD, stroke [≥1 year earlier], or carotid arterial disease) at the time of enrolment.\(^{30,31}\) Patients were assigned to either a placebo or one of three dosing regimens of atopaxar (50 mg, 100 mg, or 200 mg daily) in a ratio of 1:1:1.\(^{30,31}\) Similar to the previously mentioned trials, the investigators in the CAD trials were encouraged to follow current standard-of-care guidelines, so that placebo group patients would receive standard care.\(^{30,31}\) The primary end point of both CAD trials was the proportion of patients who experienced any bleeding event meeting CURE and TIMI criteria during the 24-week study period in both the treatment and control groups, as well as in the combined treatment group.\(^{30,31}\) The mean age of patients in the J-LANCELOT-ACS ranged between 65 and 67 years, whereas the median age of patients in the LANCELOT-ACS trial ranged between 63 to 64 years, depending on the randomized groups.\(^{30,31}\) Concurrent ASA use was 100\% in both the treatment and control groups in the Japanese trial.\(^{31}\) In the international trial, concurrent ASA use was slightly lower at 95\% in the control group and 92\% in the combined treatment group.\(^{30}\) Concurrent P2Y\(_{12}\) receptor antagonist use was 39\% in the control group and 42\% in the combined treatment group in J-LANCELOT-CAD.\(^{31}\) Very similar concurrent P2Y\(_{12}\) receptor antagonist use was observed in LANCELOT-CAD; with 36\% in the control group compared with 40\% in the combined treatment group.\(^{30}\) Bleeding results from the Japanese trial did not show a difference in CURE bleeding (0\% versus 1\%; placebo versus combined atopaxar respectively; \( P = 0.48 \)); no statistically significant difference was also observed in TIMI bleeding (any type) between these groups (4.5\% versus 9.6\%; \( P = 0.22 \)).\(^{31}\) Similarly, a dose-response relationship was not observed in CURE bleeding (\( P = 0.38 \)) and a small potential signal was observed in TIMI bleeding (\( P = 0.09 \)).\(^{31}\) Safety results from the international trial demonstrated a statistically significantly lower rate of any CURE bleeding in the placebo group compared with the combined atopaxar group (0.6\% versus 3.9\%; RR: 6.82; 95\% CI: 1.17 to 4.0; \( P = 0.03 \)).\(^{30}\) There were no statistically significant differences in the rates of any TIMI bleeding between the two groups (6.8\% versus 10.3\%; RR: 1.52; 95\% CI: 0.85 to 2.76; \( P = 0.17 \)).\(^{30}\) A trend toward more CURE bleeding across higher doses was observed (\( P = 0.01 \)); this trend was not observed for TIMI bleeding (\( P = 0.07 \)), although authors observed a general pattern of greater bleeding with a higher atopaxar dose, particularly 200 mg.\(^{30}\) Of note, most of the bleeding signals were attributed to minor (CURE) and minimal (TIMI) bleedings.\(^{30,31}\) Minimal TIMI bleeding was defined as any overt (non-CABG related) bleeding that does not meet the
criteria of major or minor bleeds, or bleeds requiring medical attention. Similar to the atopaxar ACS trials, the rates of secondary outcomes (cardiovascular death, MI, stroke, or recurrent ischemia) were non-statistically significantly different between the treatment and placebo groups in the atopaxar CAD trials. Both atopaxar CAD trials also showed liver enzyme elevation and QTc prolongation in the combined treatment group, and both effects appear to be dose-related, as well.

**Adverse Effects**

**Vorapaxar:** Bleeding is an important adverse effect of this drug. A history of stroke, TIA, intracranial hemorrhage, or any active pathological bleeding remains a contraindication for this drug because of the increased risks of intracranial hemorrhage. In addition, vorapaxar is a substrate for CYP3A4. Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole) may increase vorapaxar exposure, while use with strong CYP3A4 inducers (e.g., rifampin) may decrease exposure; such changes may potentially alter the efficacy and bleeding risks of the drug. In addition, diplopia, or double vision, was recently reported in patients on vorapaxar. The risk is small and the adverse effect appears to be reversible.

**Atopaxar:** Because this drug has yet to progress into phase 3 clinical development, limited safety data are available. The bleeding risk appears to be increased with this drug, although such risk seems to be limited to less severe bleeding complications in the phase 2 trials. Further research is needed to confirm such a pattern. A dose-dependent increase in liver enzyme abnormalities and QTc prolongation has been observed in phase 2 clinical trials. Atopaxar is also a substrate of CYP3A4 and therefore may interact with CYP3A4 inhibitors and inducers. Of note, of the six trials currently listed in the ClinicalTrials.gov database, none is a phase 3 trial, which suggests that the abnormalities noted with respect to liver enzymes and cardiac conduction in phase 2 trials may have negatively impacted the future clinical development of atopaxar.

**Administration and Cost**

Both vorapaxar and atopaxar are easy to administer, given that they are oral agents taken once daily. Therefore, patients taking these drugs are likely to be monitored in an ambulatory care setting. In terms of pricing, vorapaxar has not yet been approved in Canada, and so this information is currently unavailable. The price of vorapaxar in the US is roughly US$340 per month, but this price may not be generalizable to Canada because of differences in the health care systems, drug market characteristics, and patient demographics.

**Concurrent Developments**

There are currently no PAR-1 antagonists in clinical development as antiplatelet agents other than vorapaxar and atopaxar. Given the data available from the two large phase 3 vorapaxar trials, scholars have acknowledged that there are other potential therapeutic uses of vorapaxar based on the subgroup analyses. One author has suggested a head-to-head comparison between vorapaxar, clopidogrel, and combination ASA/dipyridamole for secondary prevention of stroke. While excess bleeding was observed in patients with a history of stroke enrolled in the TRA 2P-TIMI 50 trial, the author has argued that patients in the phase 3 trials may have been “over-treated” by the use of triple antiplatelet therapy, which led to the excessive bleeding risk. It has been suggested that removing one antiplatelet agent (e.g., the P2Y12 receptor antagonist) could improve the benefit/risk profile of vorapaxar. As previously mentioned, a recent analysis of outcomes associated with new ischemic stroke in patients enrolled in the TRA 2P-TIMI 50 study reported a reduction in the risk of first ischemic stroke with vorapaxar (HR = 0.57, 95% CI, 0.43 to 0.75; P < 0.001), compared with placebo. However, while there was no increase in the hemorrhagic conversion of these strokes, the risk of primary hemorrhagic stroke was increased (HR: 2.79, 95% CI: 1.00 to 7.73; P = 0.049). The assessment of bleeding complications will therefore be an important outcome should such a study be conducted.

Another subgroup analysis of the TRA 2P-TIMI 50 trial previously mentioned examined vorapaxar use for secondary prevention in patients with a history of both MI and diabetes. This subgroup analysis showed potential cardiovascular benefits with vorapaxar; a phase 4, open-label study is currently ongoing. This parallel-design study in post-MI patients with and without diabetes aims at assessing the pharmacodynamic effects of vorapaxar in addition to DAPT (ASA + clopidogrel), as well as in combination with clopidogrel only following ASA discontinuation. This study is expected to be completed in the fall of 2017. Also, likely based on the evidence of the benefits of vorapaxar in PAD from the TRA 2P-TIMI 50 trial, a phase 4,
randomized clinical trial is currently assessing the addition of vorapaxar on background antiplatelet therapy and standard medical therapy to improve peak-walking distance in patients with PAD and intermittent claudication. This study is also expected to be completed late 2017.45

Rate of Technology Diffusion

Where available, the uptake of PAR-1 antagonist therapy in the clinical setting may be limited because vorapaxar is considered to be an add-on drug to current antiplatelet therapy in the PAD or post-MI setting. Cardiologists are likely to be the main prescribers and must balance the additional cardiovascular benefits with the increased bleeding risks. Therefore, the use of PAR-1 antagonist therapy is currently expected to be limited to a subpopulation of CAD patients with higher cardiovascular risks. However, future research may expand the target population as more evidence emerges. Another factor which will impact the diffusion of this technology is its price and associated cost-effectiveness.

Implementation Issues

One barrier to the uptake of PAR-1 antagonist therapy is the lack of awareness among physicians of this new antiplatelet drug class. Physician-led development of clinical guideline updates will be required to not only increase PAR-1 antagonist awareness but also to promote optimal prescribing so that the benefits of treatment are favourably balanced against the increased bleeding risks. Should the PAR-1 antagonist vorapaxar be approved for clinical use in Canada, its optimal use will likely be in niche populations composed of higher-risk patients. Also, patients’ health circumstances evolve over time, and so guidance on the monitoring of patients (e.g., to assess bleeding risk) will be needed to ensure the benefit-risk ratio remains favourable.

The currently available evidence suggests that PAR-1 antagonist therapy is long term (approximately 30 months) but further clinical experience is required to more precisely determine the optimal duration of treatment during which the balance between clinical benefits and bleeding risks remains favourable. Lastly, the cost of new pharmaceuticals remains a concern, not only for public and private payers but also for patients who may have to pay for treatment out of their own pockets. Based on the price of vorapaxar in the US, the estimated annual cost per patient for this drug is roughly US$4,000.45 However, it is unclear how the American price might be extrapolated to the Canadian setting.
References


