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Rationale, Design and Baseline Characteristics of Participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial

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Cardiovascular (CV) disease is responsible for approximately one-third of deaths in persons aged 35 years or older. An estimated 17.3 million people worldwide died of CV disease in 2012 and this number is projected to increase to 23.6 million per year by 2030. Coronary artery disease (CAD) and peripheral arterial disease (PAD) are strong predictors of risk for future CV events.  

Aspirin, statins, angiotensin modulators, and β-blockers are effective and widely used for CV prevention in patients with CAD, and the first 3 classes of drugs are effective also in patients with PAD. However, despite use of these therapies, as many as 5% of patients experience recurrent vascular events each year. A more effective antithrombotic therapy than aspirin could have a major effect in further reducing the risk of nonfatal and fatal CV events in this population. 

Rivaroxaban is a selective direct coagulation factor Xa inhibitor that has been shown in large randomized controlled trials to be effective for the prevention and treatment of venous thromboembolism and for prevention of stroke or systemic embolism in patients with atrial fibrillation. In patients with a recent acute coronary syndrome, rivaroxaban given at a dose of 2.5 mg or 5 mg twice daily reduced the risk of nonfatal and fatal CV events. This vascular protective dose of rivaroxaban could be a promising option for reducing the risk of recurrent events in patients with stable CAD or PAD. 

Bleeding is the most common complication of antithrombotic therapy and predicts subsequent CV events. Although the mechanisms linking bleeding with an increased risk of CV events after bleeding remain poorly understood, prevention of bleeding can be expected to avoid related morbidity and mortality. Proton pump inhibitor treatment reduces the risk of gastrointestinal (GI) bleeding in patients treated with dual antiplatelet therapy, but has not been tested in patients treated with anticoagulant therapy.

**Evidence for efficacy of antithrombotic therapy for CV prevention in CAD and PAD**

Aspirin reduces the risk of myocardial infarction (MI), stroke, or CV death by one-fifth in patients with CAD, cerebrovascular disease, or PAD. Aspirin is also effective for prevention of graft failure after coronary artery bypass graft (CABG) surgery, but despite its use as many as 40% of patients have at least 1 obstructed graft within 1 year. Graft failure is an independent predictor of MI and death. Various antiplatelet regimens as well as warfarin have been tested as alternatives to aspirin alone for long-term secondary CV prevention. Compared with aspirin, clopidogrel produced a modest reduction in MI, stroke, or CV death, but despite its use as many as 40% of patients have at least 1 obstructed graft within 1 year. The combination of aspirin and clopidogrel did not reduce major adverse CV events compared with aspirin alone, but a benefit was evident in the subgroup of patients with a history of symptomatic disease. Long-term treatment with the combination of aspirin and dipyridamole or aspirin and ticagrelor compared with aspirin alone, or the combination of vorapaxar with standard antiplatelet therapy also yielded benefits but none of these approaches reduced mortality.

The combination of aspirin and warfarin compared with aspirin alone reduced the risk of recurrent MI in patients with a recent acute coronary syndrome but increased bleeding and did not reduce mortality. Warfarin has many drug and food interactions and its use is further complicated by the
Results: Between February 2013 and May 2016, we recruited 27,395 participants from 602 centres in 33 countries; 17,598 participants were included in the pantoprazole vs placebo comparison. At baseline, the mean age was 68.2 years, 22.0% were female, 90.6% had CAD, and 27.3% had PAD.

Conclusions: COMPASS will provide information on the efficacy and safety of rivaroxaban, alone or in combination with aspirin, in the long-term management of patients with stable CAD or PAD, and on the efficacy and safety of pantoprazole in preventing upper GI complications in patients receiving antithrombotic therapy.

The essay has been created to provide a reduction of 20% in each of the groups receiving rivaroxaban compared to acetylsalicylic acid, and a reduction of 50% of the complications of the upper digestive tract in the group receiving pantoprazole compared to placebo.

L’essai a été conçu de manière à avoir une puissance d’au moins 90 % pour déceler une réduction de 20 % dans chacun des groupes recevant le rivaroxaban comparativement à l’acide acétylsalicylique, et une réduction de 50 % des complications des voies digestives hautes dans le groupe recevant le pantoprazole comparativement au placebo.

Conclusions: L’étude COMPASS fournira des renseignements sur l’efficacité et l’innocuité du rivaroxaban, seul ou en association à l’acide acétylsalicylique, dans le traitement à long terme de patients atteints de coronaropathie ou d’artériopathie périphérique, et sur l’efficacité et l’innocuité du pantoprazole dans la prévention des complications des voies digestives hautes chez des patients recevant un traitement antithrombotique.

Specific objectives

Primary objectives for rivaroxaban randomization. The primary objectives for rivaroxaban randomization are to: (1) determine whether rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily compared with aspirin 100 mg once daily reduces the risk of the composite outcome of MI, stroke, or CV death in participants with stable CAD or PAD; and (2) determine whether rivaroxaban 5 mg twice daily compared with aspirin 100 mg once daily reduces the risk of the composite outcome of MI, stroke, or CV death in participants with stable CAD or PAD.

Secondary objectives for rivaroxaban randomization. The secondary objectives for rivaroxaban randomization are to: (1) determine whether rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily, or rivaroxaban 5 mg twice daily compared with aspirin 100 mg once daily reduces the risk of the composite of major thrombotic events (coronary heart disease death, MI, ischemic stroke, or acute limb ischemia; and CV death, MI, ischemic stroke, acute limb ischemia) in participants with stable CAD or PAD; and (2) determine whether rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily, or rivaroxaban 5 mg twice daily compared with aspirin 100 mg once daily reduces the risk of all-cause mortality in participants with stable CAD or PAD.

Main objective for pantoprazole randomization. The main objective for pantoprazole randomization was to determine whether pantoprazole 40 mg once daily compared with placebo reduces the risk of upper GI bleeding, ulceration, obstruction, or perforation in participants with stable CAD or PAD receiving antithrombotic therapy.

Prevention of upper GI events

Upper GI tract bleeding is the most common complication in patients receiving antithrombotic therapy.23-25 Proton pump inhibitors are effective for the prevention of upper GI bleeding in patients treated with dual antiplatelet therapy,10 but have not been tested in a randomized trial for prevention of GI tract complications in patients treated with anticoagulants. Observational study results have meanwhile fueled concerns that long-term proton pump inhibitor therapy might be associated with an increased risk of serious adverse outcomes, including pneumonia, enteric infection, osteoporosis, chronic kidney disease, and cognitive decline.26-28 These associations might relate to residual confounding and it is important that benefits and potential long-term safety concerns be evaluated in a randomized trial.

Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial
Study design, eligibility, and oversight

COMPASS is a phase III, event-driven, blinded, randomized controlled trial with a 3 × 2 partial factorial design that is sponsored by Bayer AG. The steering committee, comprised of Population Health Research Institute (PHRI) investigators, the National Leaders, and sponsor representatives, was responsible for development of the protocol and is responsible for the conduct and oversight of the study. The protocol was approved by institutional review boards and health authorities in all participating countries. Written informed consent was obtained from all participants.

The design is summarized in Figure 1. For the purpose of the trial, CAD was defined as previous MI or history of angina with evidence of multivessel disease, or multivessel revascularization; and PAD was defined as claudication with objective evidence of arterial disease, previous amputation or revascularization, previous carotid revascularization, or asymptomatic carotid disease with at least 50% stenosis (Table 1). Inclusion and exclusion criteria are listed in Table 2.

Run-in. During the 30-day run-in period, potentially eligible subjects (excluding those who were randomized 4-14 days after CABG surgery) received rivaroxaban placebo twice daily and aspirin 100 mg once daily. Study pantoprazole/pantoprazole placebo was not administered during the run-in.

Randomization. Subjects who successfully completed the run-in period (defined as at least 80% adherence to treatment) and who consented to continue in the study, as well as those enrolled after CABG were randomized in a 1:1 ratio to receive pantoprazole or pantoprazole placebo, if they had no continuous need for a proton pump inhibitor. All subjects were randomized in a 1:1:1 ratio to receive 1 of the 2 rivaroxaban arms vs aspirin stratified according to centre and PPI use. All subjects randomized early after CABG surgery. Participants randomized soon after CABG surgery underwent the same screening, follow-up, and washout periods as other COMPASS trial participants except that they did not undergo a run-in. The run-in was not required because thrombotic graft occlusion that can potentially be prevented by rivaroxaban is believed to occur during the first few weeks after CABG surgery and a run-in would delay the start of rivaroxaban. Most of these subjects underwent screening during the 2-3 weeks before surgery or in the days immediately after surgery and before randomization.

COMPASS CABG participants were randomized between days 4 and 14 after surgery and at least 24 hours after removal of chest tube and at least 12 hours after the last administration of any anticoagulant (including venous thromboembolism prophylaxis). All participants randomized 4-14 days after CABG surgery were required to undergo coronary computed tomography angiography to evaluate graft patency at 1 year as part of the study protocol unless they had already undergone conventional angiography as part of their usual medical care or they had a specific contraindication for computed tomography angiography (eg, contrast allergy, estimated glomerular filtration rate < 30 mL/min/1.73 m²).

Outcomes. The primary efficacy outcome for the rivaroxaban randomization is the composite of MI, stroke, or CV death. The primary safety outcome is based on a modified International Society on Thrombosis and Haemostasis (ISTH) criteria.

Table 1. COMPASS trial eligibility

| Coronary artery disease, defined as: | • Myocardial infarction within the past 20 years, or |
| • Multivessel coronary disease* with symptoms or with history of stable or unstable angina, or |
| • Multivessel percutaneous coronary intervention, or |
| • Multivessel CABG surgery |
| Peripheral arterial disease, defined as: | • Previous aortofemoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac, or infragluteal arteries, or |
| • Previous limb or foot amputation for arterial vascular disease, or |
| • History of intermittent claudication and 1 or more of the following: |
| (1) an ankle/arm blood pressure ratio < 0.90, or |
| (2) significant peripheral artery stenosis (≥50%) documented using angiography, or duplex ultrasound, or |
| (3) Previous carotid revascularization or asymptomatic carotid artery stenosis ≥50% as diagnosed using duplex ultrasound or angiography |

CABG, coronary artery bypass graft; COMPASS, Cardiovascular Outcome for People Using Anticoagulation Strategies.

* Refers to stenosis of ≥50% in 2 or more coronary arteries, confirmed using invasive coronary angiography, or noninvasive imaging or stress studies (eg, exercise or pharmacologic) suggestive of significant ischemia in ≥ 2 coronary territories; or in 1 coronary territory if at least 1 other territory has been revascularized.

Figure 1. The trial randomized 27,395 subjects with prevalent vascular disease (coronary or peripheral artery disease) in a 3 × 2 partial factorial design. (A) All subjects were randomized in a 1:1:1 ratio to receive 1 of the 2 rivaroxaban arms vs aspirin stratified according to centre and PPI use. The primary efficacy outcome for the rivaroxaban/aspirin randomization was the composite of myocardial infarction, stroke, or cardiovascular death, and the main safety outcome was major bleeding defined according to modified International Society on Thrombosis and Haemostasis (ISTH) criteria. (B) Subjects were randomized in a 1:1 ratio to receive pantoprazole or pantoprazole placebo if they had no continuous need for a proton pump inhibitor (PPI). The main outcome for the pantoprazole randomization was a composite of upper gastrointestinal tract complications. bid, twice daily; od, once daily; R, randomization.
Table 2. Eligibility criteria

Inclusion criteria
- Willing and able to provide written informed consent
- Meet criteria for CAD and/or PAD (see Table 1)
- Subjects with CAD must also meet at least 1 of the following criteria:
  - Age 65 years or older, or
  - Age younger than 65 years and documented atherosclerosis or revascularization involving at least 2 vascular beds* or at least 2 additional risk factors:
    1. Current smoker (within 1 year of randomization)
    2. Diabetes mellitus
    3. Renal dysfunction with estimated glomerular filtration rate < 60 mL/min
    4. Heart failure
    5. Nonlacunar ischemic stroke ≥ 1 month ago

Exclusion criteria
- High risk of bleeding
- Stroke within 1 month or any history of hemorrhagic or lacunar stroke
- Severe heart failure with known ejection fraction < 30% or New York Heart Association class III or IV symptoms
- Estimated glomerular filtration rate < 15 mL/min
- Need for dual antiplatelet therapy, other nonaspirin antiplatelet therapy, or oral anticoagulant therapy
- Known noncardiovascular disease that is associated with poor prognosis (eg, metastatic cancer) or that increases the risk of an adverse reaction to study interventions
- History of hypersensitivity or known contraindication for rivaroxaban, aspirin, pantoprazole, or excipients, if applicable
- Systemic treatment with strong inhibitors of CYP 3A4 as well as p-glycoprotein (eg, systemic azole antifungal agents, such as ketoconazole, and HIV-protease inhibitors, such as ritonavir), or strong inducers of CYP 3A4 (ie, ritonavir, rifamycins, phenobarbital, phenytoin, and carbamazepine)
- Any known hepatic disease associated with coagulopathy
- Subjects who are pregnant, breastfeeding, or are of childbearing potential, and sexually active and not practicing an effective method of birth control (eg, surgically sterile, prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization)
- Previous assignment to treatment during this study
- Concomitant participation in another study with investigational drug
- Known contraindication to any study-related procedures

CAD, coronary artery disease; CYP, Cytochrome P; PAD, peripheral artery disease.
* Because CAD involves disease in the coronary vasculature, only 1 additional vascular bed is required (eg, the aorta, arterial supply to the brain, gastro-intestinal tract, lower limbs, upper limbs, kidneys).
† Use of a proton pump inhibitor excluded participation in the pantoprazole randomization.

criteria and is the composite of fatal bleeding, symptomatic bleeding in a critical organ, or bleeding into the surgical site requiring reoperation, and bleeding leading to hospitalization (includes presentation to an acute care facility without overnight stay). Secondary and tertiary outcomes for the rivaroxaban/aspirin randomization are listed in Table 3.

The main outcome for the pantoprazole randomization is the composite of overt bleeding of GI origin confirmed using endoscopy or radiography, overt upper GI bleeding of unknown origin, bleeding of presumed occult GI origin with documented decrease of hemoglobin of 2 g/dL from baseline, symptomatic gastroduodenal ulcer, GI pain with underlying multiple gastroduodenal erosions, and obstruction or perforation. Safety outcomes for the pantoprazole and pantoprazole placebo arms of the study are listed in Table 4.

Definitions of study outcomes are provided in Supplemental Appendix S1.

Follow-up. Participants were seen at 1 and 6 months after randomization, and at 6-month intervals thereafter to record outcomes and adverse events, and enhance adherence. Additional follow-up visits were conducted via telephone at 3 and 9 months. Validated questionnaires were administered at randomization and at month 24 to collect data on subject health and quality of life (Standard Assessment of Global Activities in the Elderly, Montreal Cognitive Assessment, Digital Symbol Substitution, European Quality of Life-5 Dimensions, Interheart Diet Questionnaire, and the short form of the International Physical Activity Questionnaire). Functional and cognitive questionnaires were repeated at the visit after a primary outcome event and also at study end. All subjects are followed for the duration of the study irrespective of whether they received study treatments or whether an event has occurred.

The final washout period visit is being conducted by telephone 30 days after the final follow-up visit. The purpose of the washout visit is to collect information on outcomes and
Table 4. Safety outcomes for the pantoprazole randomization

<table>
<thead>
<tr>
<th>Safety outcomes</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric atrophy</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile infections</td>
<td></td>
</tr>
<tr>
<td>Other enteric infections</td>
<td></td>
</tr>
<tr>
<td>Bone fractures</td>
<td></td>
</tr>
<tr>
<td>New diagnosis since randomization of:</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td></td>
</tr>
</tbody>
</table>

Sample size. COMPASS is an event-driven trial that is designed to continue until at least 2200 participants experience a confirmed primary efficacy outcome. The originally planned sample size of 19,500 subjects was on the basis of the following assumptions for the antithrombotic treatment randomization: a 3-arm study with 1:1:1 randomization, 2-sided overall type I error level of 5%, an annual event rate of 4.0%-4.5%, and a 90% power on the basis of a 20% relative risk reduction for each of the 2 comparisons of rivaroxaban vs aspirin. The expectation for the duration of recruitment was approximately 2.5 years, and for permanent discontinuation of study drug was 6% in the first 6 months, 4% in the second 6 months, and 3% during each 6-month period thereafter. On the basis of slower than expected recruitment rate and a lower than expected aggregate incidence of the primary outcome of 2.9%, the sample size was increased to 27,400 subjects in July 2015. We projected that we would reach the target number of primary efficacy outcome events in the first quarter of 2018.

For the comparison of pantoprazole vs its placebo, we assumed an annual incidence risk for major upper GI complications of 1.6%-2.2%, and with randomization of at least 14,000 subjects to pantoprazole or pantoprazole placebo we expected that at least 500 events would accrue during follow-up, resulting in at least 90% power to detect a 50% relative risk reduction using a 2-sided type I error level of 5%.

Analyses. Analysis of the primary outcome will be based on the intention to treat principle. Comparisons will be performed between each of the rivaroxaban-based treatment and the common aspirin control group. These 2 comparisons will be performed using 2 separate stratified log rank tests. Proton pump inhibitor use will be used as a stratification factor. To address the multiplicity related to the testing of 2 primary and secondary hypotheses, a mixture gatekeeping procedure on the basis of the Hochberg test will be used to control the familywise error rate of \( \alpha = 5\% \).

Kaplan-Meier estimates of cumulative risk and cumulative hazard function will be provided to evaluate the timing of event occurrences in the 3 antithrombotic treatment groups and the consistency of the respective treatment effects at all time points. HR, relative risk reduction, and corresponding 95% confidence intervals will be estimated on the basis of 2 separate stratified Cox proportional hazards models.

Details of the statistical approach are provided in the statistical analysis plan.

Data Safety and Monitoring Board. An independent Data Safety and Monitoring Board (DSMB) is monitoring the study for safety and efficacy. Two formal interim analyses are planned to assess efficacy of the rivaroxaban/aspirin arms when approximately 50% and 75% of primary efficacy outcomes have accrued. For efficacy, the primary outcome is monitored using a modified Haybittle-Peto rule using 4 SDs for the first interim analysis and 3 SDs for the second analysis. If the observed relative risk for the primary efficacy outcome at 1 of the pre-specified interim analyses crosses the critical value obtained using the corresponding modified Haybittle-Peto boundary, another analysis will be performed 3-6 months later; if the observed relative risk again crosses the critical value then the DSMB could recommend that the trial be terminated for efficacy of rivaroxaban-based therapy. No formal boundaries were set for terminating the study for safety reasons but clear and consistent evidence of a net harm that overwhelms any benefit should be apparent. Because of the extreme nature of the monitoring boundaries, the need to cross the boundary on 2 occasions and the paucity of interim analyses, no material adjustment of the significance level of the final analysis is required.

Baseline characteristics. The trial randomized 27,395 patients from 602 centres in 33 countries between March 2013

Table 5. COMPASS participant baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant n</td>
<td>27,395</td>
</tr>
<tr>
<td>Mean age (SD), years</td>
<td>68.2 (7.94)</td>
</tr>
<tr>
<td>Male sex</td>
<td>21,375 (78)</td>
</tr>
<tr>
<td>Mean heart rate (SD), beats per minute</td>
<td>67.6 (10.65)</td>
</tr>
<tr>
<td>Mean SBP (SD), mm Hg</td>
<td>135.5 (17.57)</td>
</tr>
<tr>
<td>Mean DBP (SD), mm Hg</td>
<td>77.6 (9.98)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.3 (4.74)</td>
</tr>
<tr>
<td>ABI &lt; 0.9</td>
<td>3643 (13.3)</td>
</tr>
<tr>
<td>Mean cholesterol (SD), mmol/L</td>
<td>4.3 (3.51)</td>
</tr>
<tr>
<td>Mean creatinine (SD), µmol/L</td>
<td>90.7 (54.12)</td>
</tr>
<tr>
<td>Mean eGFR (SD), ml/min/1.73m²</td>
<td>73.8 (17.9)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>5866 (21.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20,627 (75.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10,340 (37.7)</td>
</tr>
<tr>
<td>CAD history</td>
<td>24,825 (90.6)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>17,022 (62.1)</td>
</tr>
<tr>
<td>Mean time since last MI (SD), years</td>
<td>7.1 (6.46)</td>
</tr>
<tr>
<td>Previous CABG surgery</td>
<td>6470 (23.5)</td>
</tr>
<tr>
<td>Heart failure history</td>
<td>5900 (21.5)</td>
</tr>
<tr>
<td>Stroke history</td>
<td>1033 (3.8)</td>
</tr>
<tr>
<td>PAD history</td>
<td>7470 (27.3)</td>
</tr>
<tr>
<td>Asymptomatic carotid stenosis &gt; 50%</td>
<td>1917 (7)</td>
</tr>
<tr>
<td>Peptic ulcer history</td>
<td>1237 (4.5)</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>723 (2.6)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>3918 (14.3)</td>
</tr>
<tr>
<td>South America</td>
<td>6144 (22.4)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>8555 (31.2)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>4823 (17.6)</td>
</tr>
<tr>
<td>Asia/Pacific</td>
<td>3955 (14.4)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) except where otherwise stated.

ABI, ankle brachial index; CABG, coronary artery bypass graft; CAD, coronary artery disease; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PAD, peripheral artery disease; SBP, systolic blood pressure.
Substudy: COMPASS MIND

The effect of the intervention on incident covert infarcts in the brain (i.e., infarcts unrecognized clinically but identified on cerebral imaging) will be examined in a subgroup of the brain (i.e., infarcts unrecognized clinically but identified on cerebral imaging). Details of the design of this substudy will be published separately.

Study management

The trial is independently managed by the PHRI and a Steering Committee in collaboration with the sponsor, Bayer AG. The trial is registered at www.clinicaltrials.gov (NCT01776424). Members of the Operations Committee, Steering Committee, DSMB, and the staff at the PHRI Project Office and Bayer AG involved in the conduct of the study are listed in Supplemental Appendix S2.

Discussion

The COMPASS trial tests if rivaroxaban-based therapy compared with aspirin prevents CV events and also tests if a proton pump inhibitor compared with placebo reduces upper GI complications in patients with stable CAD or PAD. Previous attempts to improve the efficacy of antithrombotic therapy for long-term secondary CV prevention using combinations of antiplatelet drugs and combinations of an antiplatelet drug and warfarin have had limited success; they did not improve efficacy or were associated with modest improvements in efficacy, excess bleeding, and no overall mortality benefit. In COMPASS, we hypothesize that the improvement in efficacy achieved with the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily or rivaroxaban 5 mg twice daily or compared with aspirin 100 mg once daily will outweigh any increase in bleeding.

The safety of antithrombotic therapy for long-term secondary prevention of CV events might be further improved by use of a proton pump inhibitor, as is being tested in the COMPASS partial factorial design.

Other unique aspects of the COMPASS trial include assessment of the effect of rivaroxaban on graft patency in COMPASS CABG and on covert brain ischemia in COMPASS MIND. CABG surgery remains the definitive treatment for patients with advanced CAD, but is limited by early graft failure. Aspirin has been proven to prevent early graft failure, but graft failure rates remain high despite its use. The COMPASS CABG substudy will test whether antithrombotic therapy with or without concomitant aspirin will improve 1-year graft patency compared with aspirin alone. The COMPASS MIND magnetic resonance imaging substudy is highly relevant because of the growing burden of unrecognized brain ischemia and related complications in the aging world population. Covert stroke is a major cause of cognitive loss, and the prevention of covert stroke using rivaroxaban might also help to prevent cognitive decline.

In conclusion, the COMPASS trial program is testing whether a vascular protective dose of rivaroxaban, with or without antiplatelet therapy with aspirin, can reduce major cardiac adverse events in patients with stable CAD and PAD. At the same time, it tests strategies to improve the safety of antithrombotic therapies by preventing GI bleeding. The results are likely to provide definitive information that will affect multiple guidelines and will change clinical practice.

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References


Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the Canadian Journal of Cardiology at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2017.06.001.