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Clinical Research

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

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ABSTRACT

Background: Long-term aspirin prevents vascular events but is only modestly effective. Rivaroxaban alone or in combination with aspirin might be more effective than aspirin alone for vascular prevention in patients with stable coronary artery disease (CAD) or peripheral artery disease (PAD). Rivaroxaban as well as aspirin increase upper gastrointestinal (GI) bleeding and this might be prevented by proton pump inhibitor therapy.

Methods: Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) is a double-blind superiority trial comparing rivaroxaban 2.5 mg twice daily combined with aspirin 100 mg once daily or rivaroxaban 5 mg twice daily vs aspirin 100 mg once daily for prevention of myocardial infarction, stroke, or cardiovascular death in patients with stable CAD or PAD. Patients not taking a proton pump inhibitor were also randomized, using a partial factorial design, to pantoprazole 40 mg once daily or placebo. The trial was designed to have at least 90% power to detect a 20% reduction in each of the rivaroxaban treatment arms compared with aspirin and to detect a 50% reduction in upper GI complications with pantoprazole compared with placebo.

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 2030.¹ Coronary artery disease (CAD) and peripheral arterial disease (PAD) are strong predictors of risk for future CV events.^{1,2}

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.³ 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.⁴⁻⁷ 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.⁸ 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.⁹ 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

RÉSUMÉ

Contexte : Un traitement à long terme par l'acide acétylsalicylique prévient les accidents vasculaires, mais son efficacité reste modeste. Le rivaroxaban seul ou en association avec l'acide acétylsalicylique serait plus efficace que l'acide acétylsalicylique seul pour prévenir les accidents vasculaires chez les patients atteints de coronaropathie ou d'artériopathie périphérique stables. Le rivaroxaban et l'acide acétylsalicylique augmentent tous deux les saignements gastro-intestinaux, et cet effet indésirable pourrait être contré à l'aide d'un inhibiteur de la pompe à protons.

Méthodes : L'essai COMPASS (*Cardiovascular Outcomes for People Using Anticoagulation Strategies*) est un essai de supériorité à double insu comparant ou le rivaroxaban à raison de 5 mg, 2 fois par jour vs l'acide acétylsalicylique à raison de 100 mg, 1 fois par jour dans la prévention de l'infarctus du myocarde, de l'accident vasculaire cérébral ou du décès d'origine cardiovasculaire chez des patients atteints de coronaropathie ou d'artériopathie périphérique stables. Les patients qui ne prenaient pas un inhibiteur de la pompe à protons ont aussi été répartis au hasard selon un plan factoriel partiel, pour recevoir le pantoprazole à raison de 40 mg, une fois par jour, ou un placebo.

treatment reduces the risk of gastrointestinal (GI) bleeding in patients treated with dual antiplatelet therapy,¹⁰ 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.¹¹ Aspirin is also effective for prevention of graft failure after coronary artery bypass graft (CABG) surgery,¹¹ but despite its use as many as 40% of patients have at least 1 obstructed graft within 1 year.¹² 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.¹³ The combination of aspirin and clopidogrel did not reduce major adverse CV events compared with aspirin alone,¹⁴ but a benefit was evident in the subgroup of patients with a history of symptomatic disease.¹⁵ 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.¹⁶⁻¹⁸

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.¹⁹⁻²¹ 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.

need for routine coagulation monitoring. In patients with PAD, the combination of aspirin and warfarin did not reduce ischemic events and markedly increased bleeding, although a benefit was suggested in an exploratory post hoc analysis that excluded patients with bleeding.²² The evidence of efficacy of warfarin after acute coronary syndrome and the suggestion of a benefit in PAD among participants who did not experience bleeding support the rationale for testing a safer and more convenient anticoagulant as an alternative to or in addition to aspirin for secondary prevention of CV events.

Rivaroxaban was tested as add-on therapy to standard of care in patients with a recent acute coronary syndrome in the **Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome - Thrombolysis In Myocardial Infarction-51 (ATLAS TIMI-51)** trial. At doses of 2.5 mg or 5 mg twice daily, rivaroxaban compared with placebo reduced the risk of MI, stroke, or CV death by 16% (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.74-0.96; $P = 0.008$) and stent thrombosis by 31% (HR, 0.69; 95% CI, 0.51-0.93; $P = 0.02$). The 2.5 mg twice daily dose also reduced total mortality (HR, 0.68; 95% CI, 0.53-0.87; $P = 0.002$).⁸ Most participants ($n = 14,473$) also received the combination of aspirin and clopidogrel, and this might explain the increase in major and intracranial bleeding with both doses of rivaroxaban, and especially with the 5-mg twice daily dose. On a background of aspirin alone ($n = 1053$), rivaroxaban compared with placebo produced consistent benefits and appeared to be associated with no excess of major bleeding.

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 therapy¹⁰ 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,

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.

Résultats : De février 2013 à mai 2016, nous avons recruté 27 395 participants de 602 centres dans 33 pays; 17 598 participants ont été inclus dans la comparaison entre le pantoprazole et le placebo. Au départ, l'âge moyen était de 68,2 ans, 22,0 % des patients étaient des femmes, 90,6 % étaient atteints de coronaropathie et 27,3 % d'artériopathie périphérique.

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 stables, 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.

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

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.

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)

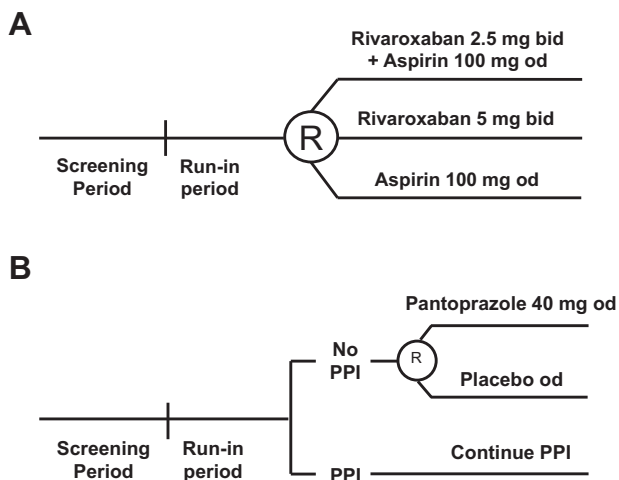


Figure 1. The trial randomized 27,395 subjects with prevalent vascular disease (coronary or peripheral artery disease) in a 3×2 partial factorial design. **(A)** All subjects were randomized in a 1:1:1 ratio to receive 1 of the 2 rivaroxaban arms vs aspirin stratified according to centre and PPI use. 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 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 infrainguinal 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 ($\geq 50\%$) documented using angiography, or duplex ultrasound, or
(3) Previous carotid revascularization or asymptomatic carotid artery stenosis $\geq 50\%$ as diagnosed using duplex ultrasound or angiography

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

* Refers to stenosis of $\geq 50\%$ 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.

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 in a 1:1:1 ratio stratified according to centre and proton pump inhibitor use.

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 modification of the International Society on Thrombosis and Haemostasis (ISTH)

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 antimycotics, such as ketoconazole, and HIV-protease inhibitors, such as ritonavir), or strong inducers of CYP 3A4 (ie, rifampicin, rifabutin, 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 3. Secondary and tertiary outcomes for the rivaroxaban/aspirin randomization

Secondary outcomes
• Coronary heart disease death, myocardial infarction, ischemic stroke, acute limb ischemia
• Cardiovascular death, myocardial infarction, ischemic stroke, acute limb ischemia
• All-cause mortality
Tertiary
• Subject-reported Standard Assessment of Global Activities in the Elderly, Montreal Cognitive Assessment, Digital Symbol Substitution, European Quality of Life-5 Dimensions, Interheart Diet Questionnaire, International Physical Activity Questionnaire
• Individual components of the primary and secondary outcomes
• Hospitalization for cardiovascular reasons
• All-cause hospitalizations
• Arterial revascularization
• Limb amputation
• Stent thrombosis
• Unstable angina
• Worsening angina
• New angina
• New heart failure
• Venous thromboembolic events
• Resuscitated cardiac arrest
• New diagnosis of cancer

Table 4. Safety outcomes for the pantoprazole randomization

Safety outcomes
• Gastric atrophy
• Pneumonia
• Clostridium difficile infections
• Other enteric infections
• Bone fractures
New diagnosis since randomization of:
• Chronic kidney disease
• Diabetes
• Chronic obstructive lung disease
• Dementia

protocol-specific adverse events that might occur after discontinuation of investigational treatment.

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 in the aspirin control group of 4.0%–4.5%,^{3,29} 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%,¹⁰ 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 $\alpha = 5\%$.³⁰

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

Characteristic	Value
Participant n	27,395
Mean age (SD), years	68.2 (7.94)
Male sex	21,375 (78)
Mean heart rate (SD), beats per minute	67.6 (10.65)
Mean SBP (SD), mm Hg	135.5 (17.57)
Mean DBP (SD), mm Hg	77.6 (9.98)
Body mass index	28.3 (4.74)
ABI < 0.9	3643 (13.3)
Mean cholesterol (SD), mmol/L	4.3 (3.51)
Mean creatinine (SD), $\mu\text{mol/L}$	90.7 (54.12)
Mean eGFR (SD), mL/min/1.73m ²	73.8 (17.9)
Current smoking	5866 (21.4)
Hypertension	20,627 (75.3)
Diabetes	10,340 (37.7)
CAD history	24,825 (90.6)
Previous MI	17,022 (62.1)
Mean time since last MI (SD), years	7.1 (6.46)
Previous CABG surgery	6470 (23.5)
Heart failure history	5900 (21.5)
Stroke history	1033 (3.8)
PAD history	7470 (27.3)
Asymptomatic carotid stenosis > 50%	1917 (7)
Peptic ulcer history	1237 (4.5)
Bleeding requiring transfusion	723 (2.6)
Region	
North America	3918 (14.3)
South America	6144 (22.4)
Western Europe	8555 (31.2)
Eastern Europe	4823 (17.6)
Asia/Pacific	3955 (14.4)

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.

and May 2016. Baseline characteristics of the participants are presented in [Table 5](#). The mean age at enrollment was 68.2 years, 22.0% were female, 90.6% had a history of CAD, and 27.3% had a history of PAD. A total of 1448 subjects were randomized within 4-14 days after CABG surgery and 17,598 were randomized to pantoprazole or pantoprazole placebo.

Substudy: COMPASS MIND

The effect of the intervention on incident covert infarcts in the brain (ie, infarcts unrecognized clinically but identified on cerebral imaging)³¹ will be examined in a subgroup of COMPASS participants with baseline magnetic resonance 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 guidelines³²⁻³⁴ and will change clinical practice.

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References

- Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016;133:e38-360.
- Hankey GJ, Norman PE, Eikelboom JW. Medical treatment of peripheral arterial disease. *JAMA* 2006;295:547-53.
- Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010;304:1350-7.
- Turpie AG, Lassen MR, Eriksson BI, et al. Rivaroxaban for the prevention of venous thromboembolism after hip or knee arthroplasty. Pooled analysis of four studies. *Thromb Haemost* 2011;105:444-53.
- Buller HR, Prins MH, Lensing AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287-97.
- Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499-510.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.
- Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;366:9-19.
- Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J* 2011;32:1854-64.
- Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010;363:1909-17.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [erratum in: 2002;324:141]. *BMJ* 2002;324:71-86.
- Alexander JH, Haffley G, Harrington RA, et al. Efficacy and safety of edifoligide, an E2F transcription factor decoy, for prevention of vein graft failure following coronary artery bypass graft surgery: PREVENT IV: a randomized controlled trial. *JAMA* 2005;294:2446-54.
- A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348:1329-39.
- Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.
- Bhatt DL, Flather MD, Hacke W, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 2007;49:1982-8.
- Li X, Zhou G, Zhou X, Zhou S. The efficacy and safety of aspirin plus dipyridamole versus aspirin in secondary prevention following TIA or stroke: a meta-analysis of randomized controlled trials. *J Neurol Sci* 2013;332:92-6.
- Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;372:1791-800.
- Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012;366:1404-13.
- Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. *N Engl J Med* 2002;347:969-74.
- van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet* 2002;360:109-13.
- Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. *J Am Coll Cardiol* 2003;41(4 suppl S):62S-9S.
- Anand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med* 2007;357:217-27.
- Derry S, Loke YK. Risk of gastrointestinal hemorrhage with long term use of aspirin: meta-analysis. *BMJ* 2000;321:1183-7.

24. Lanas A, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis. *Clin Gastroenterol Hepatol* 2011;9:762-8.
25. Lanas A, Carrera-Lasfuentes P, Arguedas Y, et al. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. *Clin Gastroenterol Hepatol* 2015;13:906-12.
26. Moayyedi P, Leontiadis GI. The risks of PPI therapy. *Nat Rev Gastroenterol Hepatol* 2012;9:132-9.
27. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med* 2016;176:238-46.
28. Gomm W, von Holt K, Thomé F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol* 2016;73:410-6.
29. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547-59.
30. Brechenmacher T, Xu J, Dmitrienko A, Tamhane AC. A mixture gate-keeping procedure based on the Hommel test for clinical trial applications. *J Biopharm Stat* 2011;21:748-67.
31. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol* 2007;6:611-9.
32. Bell AD, Roussin A, Cartier R, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society guidelines. *Can J Cardiol* 2011;27(suppl A):S1-59.
33. Macle L, Cairns J, Leblanc K, et al. 2016 Focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. *Can J Cardiol* 2016;32:1170-85.
34. Rodriguez F, Mahaffey KW. Management of patients with NSTEMI-ACS: a comparison of the recent AHA/ACC and ESC Guidelines. *J Am Coll Cardiol* 2016;68:313-21.

Supplementary Material

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