News Release

In Canadian-Led Phase III Clinical Study, Xarelto® when Combined with ASA Significantly Lowered the Combined Risk of Stroke, Cardiovascular Death, and Heart Attack in Patients with Chronic Coronary or Peripheral Artery Disease by 24%

- Rivaroxaban vascular dose, 2.5 mg twice daily, plus acetylsalicylic acid (ASA), 100 mg once daily, showed an unprecedented 42% relative risk reduction in stroke and 22% in cardiovascular death compared with ASA 100 mg once daily alone.
- Bleeding rates were low, and while major bleeding was increased, notably, there was no significant increase in intracranial or fatal bleeding.
- This combination regimen demonstrated a substantial improvement in net clinical benefit of 20%.
- Data from Canadian-led COMPASS study, revealed at ESC Congress 2017, included 27,395 patients globally and 50 trial sites in Canada.
- The indication for the prevention of major cardiac events (MACE) in patients with coronary artery disease (CAD) or periphery artery disease (PAD) is not yet approved in Canada.

Toronto, Ontario (August 28, 2017) – In the Phase III COMPASS study, the vascular dose (2.5 mg twice daily) of Bayer’s Factor Xa inhibitor, rivaroxaban (Xarelto®), plus acetylsalicylic acid (ASA) 100 mg once daily, reduced the risk of the composite outcome of stroke, cardiovascular (CV) death, and heart attack by 24% (relative risk reduction) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).

The study compared this combined approach with ASA 100 mg once daily alone. Patients included in the study had already received guideline recommended therapy for hypertension, high cholesterol and diabetes. A 5 mg twice daily dose of rivaroxaban was also investigated but the difference in the primary outcome did not reach statistical significance. Data were revealed during two Hot Line presentations at ESC Congress...
2017 in Barcelona, Spain, August 26-30. The COMPASS findings were simultaneously published in *The New England Journal of Medicine*.

The benefit shown in the combined efficacy endpoint, major adverse cardiovascular events (MACE), for rivaroxaban 2.5 mg twice daily plus ASA 100 mg once daily was mainly driven by a significant reduction of stroke (42%) and CV death (22%)\(^1\). The regimen also reduced the risk of heart attack by 14%; however, this result was not statistically significant\(^1\). This combination regimen demonstrated a substantial 20% improvement in net clinical benefit, defined as the reduction in stroke, CV death, and heart attack balanced against the most serious bleeding events\(^1\). The hazard ratio for all-cause mortality was 0.82 (95% CI 0.71-0.96; \(P=0.01\))\(^1\). Bleeding incidence rates were low, and while there was an increase in major bleeding, notably, there was no significant increase in fatal or intracranial bleeding\(^1\). Importantly, in the PAD patient population, the combination of major adverse limb events plus all major amputations of a vascular cause were reduced significantly\(^1\).

**Disease/Study Background**

Cardiovascular disease, which includes CAD and PAD, is responsible for approximately 17.7 million deaths every year, representing 31% of all global deaths\(^2\). In Canada, approximately 6% of Canadians 20 years and older live with a cardiovascular disease\(^3\). Additionally, patients with cardiovascular disease have a reduction in life expectancy of over seven years\(^4\). CAD and PAD are caused by atherosclerosis, a chronic, progressive disease which is characterized by a build up of plaque in the arteries\(^5,6\). Patients with these conditions are at risk of developing blood clots which may lead to disability, loss of limb and loss of life\(^6,7,8\).

“CAD and PAD remain a major public health burden. Despite the routine use of guideline-recommended antiplatelet therapy, event rates remain substantial,” said Dr. John Eikelboom, co-principal investigator for COMPASS and Associate Professor, Division of Hematology & Thromboembolism, Department of Medicine, McMaster University, Canada. “These findings for the vascular dose of rivaroxaban are arguably the most significant in antithrombotic therapy in this disease area to date. If approved for CAD and PAD in Canada, this vascular dose provides us with a major opportunity to change clinical practice and better treat patients.”
“Bayer has a long and successful heritage in cardiology and our medicines have already improved the lives of millions of patients across the world,” said Dr. Joerg Moeller, Member of the Executive Committee of Bayer AG's Pharmaceutical Division and Head of Development. “The COMPASS study is the first of its kind; no other NOAC has been studied in this patient population and the magnitude of these results clearly shows the benefit rivaroxaban could bring to patients with CAD or PAD. We will now work with regulatory authorities to make this treatment option available to patients as soon as possible.”

About COMPASS
The COMPASS study is the largest clinical study of rivaroxaban to date, with 27,395 patients in more than 600 research sites across more than 30 countries worldwide, including 50 in Canada. The Canadian-led study was conducted in collaboration with Hamilton-based Population Health Research Institute (PHRI), Canada’s premiere health research institute and a world leader in large clinical trials and population studies. The study was stopped approximately one year ahead of schedule due to overwhelming efficacy. Bayer, Janssen and PHRI are working towards offering rivaroxaban to study participants in an open-label extension trial. Rivaroxaban is the only non-vitamin K antagonist oral anticoagulant (NOAC) investigated in secondary prevention for cardiovascular disease in stable / chronic CAD or PAD patients.

The COMPASS study evaluated the use of rivaroxaban for the prevention of major adverse cardiac events (MACE) including CV death, myocardial infarction (MI) and stroke in patients with coronary artery disease, peripheral artery disease or both.

Patients received a run-in of ASA 100 mg once daily for 30 days, and were then randomized in a 1:1:1 ratio to receive (with or without pantoprazole):

- Rivaroxaban 2.5 mg twice daily plus ASA 100 mg once daily
- Rivaroxaban 5 mg twice daily
- ASA 100 mg once daily

Patients who were being treated with a proton pump inhibitor (PPI) prior to enrollment continued with their existing medication. Patients without a continued need for PPI treatment were randomized to pantoprazole or its placebo.
COMPASS is part of the extensive clinical research development program for rivaroxaban which, by the time of completion, will include more than 275,000 patients in clinical trials and real-world studies. In addition to COMPASS, Bayer is investigating rivaroxaban in other studies in the cardiovascular field including VOYAGER PAD and COMMANDER-HF\textsuperscript{10,11}.

**Efficacy Outcomes\textsuperscript{1}**

For the primary efficacy outcome, rivaroxaban 2.5 mg twice daily plus ASA 100 mg once daily was superior to ASA 100 mg once daily alone for the prevention of the composite endpoint of stroke, CV death and MI (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.66-0.86; P<0.001). Rivaroxaban 2.5 mg twice daily plus ASA 100 mg once daily reduced the risk of stroke by 42% (HR 0.58; 95% CI 0.44-0.76; P<0.001), CV death by 22% (HR 0.78; 95% CI 0.64-0.96; P=0.02) and heart attack by 14% (HR 0.86; 95% CI 0.70-1.05; P=0.14). Rivaroxaban 5 mg twice daily also reduced the composite outcome of stroke, CV death and MI but these results were not statistically significant.

Rivaroxaban 2.5 mg twice daily plus ASA 100 mg once daily alone improved the net clinical benefit defined as the composite of stroke, CV death, MI, fatal bleeding, or symptomatic bleeding in a critical organ (HR 0.80; 95% CI 0.70-0.91; P<0.001). Rivaroxaban 5 mg twice daily compared with ASA 100 mg once daily did not improve the net clinical benefit.

**Safety Outcomes\textsuperscript{1}**

The main safety outcome was a modification of the International Society on Thrombosis and Haemostasis (ISTH) criteria for major bleeding, and included fatal bleeding, symptomatic bleeding in a critical organ, bleeding into a surgical site requiring reoperation, and bleeding leading to hospitalization (including presentation to an acute care facility without overnight stay). Unlike the ISTH criteria, all bleeding leading to presentation to an acute care facility or hospitalization was considered as major.

Rivaroxaban 2.5 mg twice daily plus ASA 100 mg once daily compared with ASA 100 mg once daily alone increased the risk of major bleeding (HR 1.70, 95% CI 1.40-2.05, P<0.001). Most of the major bleeding was into the gastrointestinal tract, with no significant increase in fatal bleeds, intracranial bleeds or symptomatic bleeds into a critical organ.
Although there was also a significant increase in major bleeding as defined using the non-modified ISTH scale, incidence rates using this definition were approximately one-third lower when compared to those obtained when using the modified ISTH criteria.

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About Xarelto® (Rivaroxaban)
Rivaroxaban is a non-vitamin K antagonist oral anticoagulant (NOAC) and is marketed under the brand name Xarelto®. Xarelto is approved for three indications in Canada:

- The prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery.
- The treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.
- The prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.

The following indication is not approved in Canada: The prevention of major cardiac events (MACE) in patients with coronary artery disease (CAD) or periphery artery disease (PAD).

While licences may differ from country to country, across all indications Xarelto is approved in more than 130 countries.

Rivaroxaban was discovered by Bayer, and is being jointly developed with Janssen Research & Development, LLC. Xarelto is marketed outside the U.S. by Bayer and in the U.S. by Janssen Pharmaceuticals, Inc. (Janssen Research & Development, LLC and Janssen Pharmaceuticals, Inc. are part of the Janssen Pharmaceutical Companies of Johnson & Johnson).

Anticoagulant medicines are potent therapies used to prevent or treat serious illnesses and potentially life-threatening conditions. Before initiating therapy with anticoagulant medicines, physicians should carefully assess the benefit and risk for the individual patient.
Responsible use of Xarelto is a very high priority for Bayer, and the company has developed a Prescribers Guide for physicians and a Xarelto Patient Card for patients to support best practice.

**Bayer: Science For A Better Life**

Bayer is a global enterprise with core competencies in the Life Science fields of health care and agriculture. Its products and services are designed to benefit people and improve their quality of life. At the same time, the Group aims to create value through innovation, growth and high earning power. Bayer is committed to the principles of sustainable development and to its social and ethical responsibilities as a corporate citizen. In fiscal 2016, the Group employed around 115,200 people and had sales of EUR 46.8 billion. Capital expenditures amounted to EUR 2.6 billion, R&D expenses to EUR 4.7 billion. These figures include those for the high-tech polymers business, which was floated on the stock market as an independent company named Covestro on October 6, 2015. For more information, go to [www.bayer.com](http://www.bayer.com).

**The Population Health Research Institute (PHRI)**

The Population Health Research Institute (PHRI) is a joint Research Institute of McMaster University and Hamilton Health Sciences Corporation. It is Canada’s premiere global health research institute and a world leader in large clinical trials and population studies. Originally formed with a focus on cardiovascular disease and diabetes, PHRI’s research areas have broadened to include population genomics, perioperative medicine and surgery, stroke, thrombosis, renal disease, and obesity, with unparalleled expertise in epidemiology, population health and clinical trials. For more information, please visit [www.phri.ca](http://www.phri.ca).

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Forward-Looking Statements
This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer’s public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

4 Bakhai A. The burden of coronary, cerebrovascular and peripheral arterial disease. Pharmacoeconomics 2004;22:11–18