

How can the results of the COMPASS trial benefit patients with coronary or peripheral artery disease in Poland?

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KEY WORDS

COMPASS trial, coronary artery disease, major adverse cardiovascular event, peripheral artery disease, rivaroxaban

ABSTRACT

Aspirin decreases the risk of recurrent thrombotic events in patients with coronary artery disease or peripheral artery disease but the risk of recurrent events remains high. Long-term dual antiplatelet therapy or the combination of aspirin and warfarin further reduces the risk of recurrent events, but at the cost of increased bleeding, and neither of these treatments reduce mortality. The COMPASS (Cardiovascular Outcomes in People Using Anticoagulation Strategies) randomized controlled trial involving 27 395 patients from 602 sites in 33 countries (Poland: 9 sites, 518 patients) tested whether low-dose anticoagulant therapy with the coagulation factor Xa inhibitor rivaroxaban given alone or combined with aspirin reduced thrombotic risk compared with aspirin in patients with apparently stable chronic coronary and/or peripheral artery disease. In patients treated with the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily, compared with aspirin alone, the primary outcome of the composite of cardiovascular death, stroke, or myocardial infarction was decreased by 24% (hazard ratio, 0.76; 95% confidence interval, 0.66 to 0.86; $P < 0.001$), and mortality by 18% at the cost of a 70% increase in major bleeding but no significant increase in fatal or intracranial bleeding. Results were consistent in patients with coronary artery disease or peripheral artery disease, and the greatest absolute benefit was evident in the highest risk patients, including those with polyvascular disease, mild or moderate heart failure, chronic kidney disease, or diabetes. These results establish the combination of low-dose rivaroxaban and aspirin as a highly effective treatment to decrease morbidity and mortality rates in patients with atherosclerotic vascular disease.

Introduction Cardiovascular (CV) disease affects more than 300 million people and is the leading cause of death worldwide.¹ Life expectancy at birth in Poland was 77.5 years in 2015, which is more than 3 years shorter than the European Union average. The higher mortality rates in Poland appear to be explained primarily by CV mortality, which remains high despite a reduction in CV disease mortality over the past 10 years.^{2,3} Aspirin is widely used for long-term secondary prevention of CV disease because it reduces major adverse CV events (MACEs) by 19% and mortality by 10%.⁴ Several antithrombotic regimens tested as alternatives to aspirin have

further reduced nonfatal CV events, but none have significantly reduced mortality.^{5,6} Furthermore, even with antiplatelet drug combinations, patients with a history of myocardial infarction (MI) have substantial residual thrombotic risk.⁵

Rivaroxaban is a direct oral anticoagulant that targets coagulation factor Xa. In the ATLAS ACS-2 TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51) trial, low-dose rivaroxaban (2.5 mg twice daily) compared with placebo on a background of single or dual antiplatelet therapy decreased MACE

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TABLE 1 Cardiovascular-disease related mortality and morbidity rates in European countries³ (continued on the next page)

Country	Mortality			Estimated DALY	
	Latest year	Women	Men	Women	Men
Albania	2004	724.5	950.7	98	102
Armenia	2012	743.9	946.5	NR	NR
Austria	2014	348.0	457.1	58	63
Azerbaijan	2007	944.7	1078.1	65	85
Belarus	2011	726.9	1448.0	136	194
Belgium	2012	252.9	357.1	46	56
Bosnia and Herzegovina	2011	805.2	918.6	92	109
Bulgaria	2012	959.6	1299.5	149	187
Croatia	2013	581.2	761.4	87	102
Cyprus	2012	343.9	428.8	31	42
Czech Republic	2013	538.2	747.6	76	94
Denmark	2012	229.9	337.6	37	49
Estonia	2012	572.4	920.3	95	126
Finland	2013	295.6	480.7	51	76
France	2011	174.1	275.2	36	44
Georgia	2014	608.7	891.6	130	159
Germany	2013	362.1	477.2	62	72
Greece	2012	391.3	485.0	69	85
Hungary	2013	646.3	921.3	102	128
Iceland	2009	297.5	441.6	28	35
Ireland	2012	290.2	420.5	29	40
Israel	2013	194.9	255.0	23	28
Italy	2012	290.0	393.8	51	57
Kazakhstan	2012	437.5	779.9	103	146
Kyrgyzstan	2013	1087.4	1443.9	64	89
Latvia	2012	718.6	1156.8	134	177
Lithuania	2012	706.4	1096.9	105	137
Luxembourg	2013	254.9	332.7	36	41
Malta	2014	317.0	407.7	44	58
Montenegro	2009	829.4	922.3	110	114
The Netherlands	2013	233.5	332.0	38	46
Norway	2013	235.1	334.7	38	46
Poland	2013	505.6	756.0	74	106
Portugal	2013	259.7	347.0	43	52
Republic of Moldova	2013	1071.6	1380.2	131	155
Romania	2012	903.9	1143.9	111	139
Russian Federation	2011	914.0	1423.1	150	217
San Marino	2005	322.0	516.6	NR	NR
Serbia	2013	836.4	990.9	111	125
Slovakia	2010	758.5	1048.1	81	107
Slovenia	2010	390.6	532.9	53	58

and mortality with an acceptable bleeding profile.⁷ The mean duration of treatment in the ATLAS ACS-2 TIMI 51 trial was 13.1 months with a maximum follow up of 31 months.

Building on the findings of the ATLAS ACS-2 TIMI 51 study, the COMPASS (Cardiovascular Outcomes in People Using Anticoagulation Strategies) trial tested the hypothesis that long-term treatment with rivaroxaban, given alone or in combination with aspirin, would be superior to aspirin for the prevention of MACE, major adverse limb events (MALEs), and mortality in patients with apparently stable chronic coronary artery disease (CAD) or peripheral artery disease (PAD). In a second partial factorial design, the COMPASS trial also tested whether pantoprazole, a proton pump inhibitor, compared with placebo reduced upper gastrointestinal bleeding in patients with stable CAD or PAD who were not already treated with a proton pump inhibitor.⁸ The main results of COMPASS demonstrated that the combination of rivaroxaban and aspirin, compared with aspirin alone, reduced the risk of both MACE and mortality, whereas rivaroxaban alone was not superior to aspirin. Pantoprazole compared with placebo did not reduce upper gastrointestinal tract complications, defined as the composite of overt bleeding, upper gastrointestinal bleeding from a gastroduodenal lesion or of unknown origin, occult bleeding, symptomatic gastroduodenal ulcer or 5 or more erosions, upper gastrointestinal obstruction, or perforation.⁹

In this paper, we consider the potential impact of the combination of rivaroxaban and aspirin on the burden of CV disease in Poland. The specific objectives of this paper are: to 1) review the burden of CV disease in Poland; 2) summarize the new evidence from the COMPASS trial concerning the efficacy and safety of the combination of rivaroxaban and aspirin for long-term prevention of MACE in patients with chronic CAD or PAD; and 3) provide practical information on managing patients with CAD or PAD in Poland in light of these results.

Burden of cardiovascular disease in Poland

CV disease was the cause of an estimated 384 500 years lived with disability and 182 000 deaths in Poland in 2016.^{10,11} The introduction of a national public health program in Poland in the 1990s, and a corresponding increase in the number of cardiology units and angioplasty procedures was associated with a decrease in CV disease mortality from 52% of all deaths in 1990, to 46% of all deaths in 2000, and 44% of all deaths in 2010.¹² At the same time, the average life expectancy in Poland has increased from 75.2 years for women and 66.2 years for men in 1990, to 81.8 years for women and 74.0 years for men in 2017.¹³ Despite these advances, CV disease remains a major cause of morbidity and mortality

TABLE 1 Cardiovascular-disease related mortality and morbidity rates in European countries³ (continued from the previous page)

Country	Mortality			Estimated DALY	
	Latest year	Women	Men	Women	Men
Spain	2013	221.5	292.4	39	48
Sweden	2013	292.3	414.8	50	60
Switzerland	2013	242.0	339.2	37	44
Tajikistan	2004	920.0	1332.5	57	52
FYR Macedonia	2010	1012.5	1228.8	NR	NR
Turkey	2013	458.2	582.7	53	72
Turkmenistan	1998	1300.0	1748.3	104	150
Ukraine	2012	1065.8	1544.9	177	214
United Kingdom	2013	227.9	334.3	39	53
Uzbekistan	2005	1225.1	1492.4	74	89

Mortality is expressed as age-standardized mortality rate. Estimated DALY per 1000 population data is from 2012.

Abbreviations: DALY, disability adjusted life years; FYR, the former Yugoslav Republic of; NR, not reported

TABLE 2 Definitions of eligibility criteria from the COMPASS trial⁸ (continued on the next page)

CAD is defined as
Myocardial infarction within the last 20 years, or
Multivessel coronary disease ^a with symptoms or with history of stable or unstable angina, or
Multivessel percutaneous coronary intervention, or
Multivessel coronary artery bypass graft surgery
PAD is defined as
Previous aortofemoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac, or infra-inguinal arteries, or
Previous limb or foot amputation for arterial vascular disease, or
History of intermittent claudication and ≥ 1 of the following:
– An ankle/arm blood pressure ratio < 0.90 , or
– Significant peripheral artery stenosis ($\geq 50\%$) documented by angiography, or duplex ultrasound, or
– Previous carotid revascularization or asymptomatic carotid artery stenosis $\geq 50\%$ as diagnosed by duplex ultrasound or angiography
Inclusion criteria
Willing and able to provide written informed consent
Criteria for CAD and PAD met
Patients with CAD must also meet at least 1 of the following criteria:
– Age ≥ 65 , or
– Age < 65 and documented atherosclerosis or revascularization involving at least 2 vascular beds ^b or at least 2 additional risk factors
– Current smoker (within 1 year of randomization)
– Diabetes mellitus
– Renal dysfunction with estimated glomerular filtration rate < 60 ml/min
– Heart failure
– Nonlacunar ischemic stroke ≥ 1 month ago

in Poland and is the leading cause of the number of years of life lost.^{14,15} Compared with the country with the highest life expectancy in Europe in 2017, life expectancy for women in Poland was 4.7 years lower (ranked twenty-fifth) and for men was 7.8 years lower (ranked twenty-eight).¹³ Reduced life expectancy in Poland has numerous possible mechanisms, including a high prevalence of CV disease risk factors and lack of sufficient focus on early detection of atherosclerotic disease including PAD. Thus, patients with CV disease in Poland could benefit from a new strategy to reduce the risk of MACE, MALE, and mortality. The burden of CV disease in Poland is shown and compared with other European countries in TABLE 1.

Design of the COMPASS trial COMPASS was a multicenter, double-blind, double-dummy, superiority trial that included patients with a history of apparently stable chronic atherosclerotic vascular disease.¹⁶ Patients were eligible if they had a history of CAD and/or PAD. The definitions of CAD and PAD, as well as inclusion and exclusion criteria, are shown in TABLE 2. Eligible patients were randomized to the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily, rivaroxaban 5 mg twice daily (and placebo aspirin), or aspirin 100 mg once daily (and placebo rivaroxaban).

The rivaroxaban doses of 2.5 mg and 5 mg twice daily were chosen based on the results of the ATLAS ACS 2-TIMI 51 trial, in which rivaroxaban 2.5 mg twice daily, compared with placebo, on a background of standard antiplatelet therapy, reduced MACE (9.1% versus 10.7%; hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.72–0.97), increased thrombolysis in myocardial infarction major bleeding (1.8% vs 0.6%; HR, 3.46; 95% CI, 2.08–5.77) and reduced mortality (2.9% vs 4.5%; HR, 0.68; 95% CI, 0.53–0.87) in patients with recent acute coronary syndrome. Rivaroxaban 5 mg twice daily also reduced MACE and increased bleeding, but did not significantly reduce mortality.⁷

The primary outcome of COMPASS was the composite of CV death, stroke, and MI. The secondary outcomes were 1) ischemic stroke, MI, acute limb ischemia (ALI), or death from coronary heart disease; 2) ischemic stroke, MI, ALI, or CV death; 3) death from any cause. MALE was defined as ALI (limb-threatening ischemia which is confirmed by limb hemodynamics or imaging and leads to acute vascular intervention, peripheral artery surgery/reconstruction, or peripheral angioplasty/stent or amputation) or chronic limb ischemia (continuing ischemic limb, foot, or digit pain leading to hospitalization and intervention and not meeting the definition of ALI, or Fontaine stage III or IV at baseline with peripheral intervention during the course of the trial). The main safety

TABLE 2 Definitions eligibility criteria from the COMPASS trial⁸ (continued from the previous page)

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 NYHA 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 both cytochrome P450 CYP3A4 isozyme and p-glycoprotein (eg, systemic azole antimycotics, such as ketoconazole, and HIV-protease inhibitors, such as ritonavir), or strong inducers of CYP3A4, ie, rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine
Any known hepatic disease associated with coagulopathy
Patients 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
An additional exclusion for the pantoprazole randomization is the need for continuous treatment with a proton pump inhibitor

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

b Because CAD involves disease in the coronary vasculature, only one additional vascular bed is required; eg, the aorta, arterial supply to the brain, gastro-intestinal tract, lower limbs, upper limbs, kidneys

Abbreviations: CAD, coronary artery disease; PAD, peripheral artery disease; NYHA, New York Heart Association

outcome was based on a modification of the International Society on Thrombosis and Haemostasis definition of major bleeding, and included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization.^{16,17} The net clinical benefit outcome was a composite of the primary outcome, fatal bleeding, or symptomatic bleeding into a critical organ.

A total of 27 395 patients from 602 centers in 33 countries, including 518 patients from 9 sites in Poland, were randomized to one of the 3 intervention arms in a 1:1:1 ratio. Prior to randomization, potentially eligible patients had to successfully complete a 30-day run-in phase during which they were adherent to aspirin and rivaroxaban placebo at least 80% of the time.

At baseline, the median age of participants was 68.2 years, 22% were women, 75% had

a history of hypertension, 38%, a history of diabetes, 3.8%, a prior stroke, and 62%, a previous MI. A high proportion of patients enrolled in the trial were receiving other proven secondary prevention therapies. Lipid-lowering agents were used in 90% of patients, angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker in 71%, β -blockers in 70%, and diuretics in 29%. The patients included in COMPASS are comparable to those enrolled in prior trials testing alternatives to aspirin for long-term prevention of CV events.

Results of the COMPASS trial The combination of rivaroxaban and aspirin, compared with aspirin, reduced the primary outcome by 24% (absolute risk, 4.1% vs 5.4%; HR, 0.76; 95% CI, 0.66–0.86; $P < 0.001$) and mortality by 18% (absolute risk, 3.4% vs 4.1%; HR, 0.82; 95% CI, 0.71–0.96; $P = 0.01$), as shown in TABLE 3. Each of the components of the primary outcome was reduced, including CV death by 22% (absolute risk, 1.7% vs 2.2%; HR, 0.78; 95% CI, 0.64–0.96; $P = 0.02$), stroke by 42% (absolute risk, 0.9% vs 1.6%; HR, 0.58; 95% CI, 0.44–0.76; $P < 0.001$), and MI by 14% (absolute risk, 1.9% vs 2.2%; HR, 0.86; 95% CI, 0.70–1.05; $P = 0.14$). The combination also reduced MALE (HR, 0.54; 95% CI, 0.35–0.84; $P = 0.0054$). These benefits were achieved at the cost of an increase in major bleeding (absolute risk, 3.1% vs 1.9%; HR, 1.70; 95% CI, 1.40–2.05; $P < 0.001$) and primarily gastrointestinal bleeding (absolute risk, 1.5% vs 0.7%; HR, 2.15; 95% CI, 1.60–2.89; $P < 0.001$). There was no significant increase in fatal or critical organ bleeding, and the combination produced a significant net clinical benefit (absolute risk, 4.7% vs 5.9%; HR, 0.80; 95% CI, 0.70–0.91; $P < 0.001$).^{8,18,19} There was no significant benefit of rivaroxaban alone compared with aspirin.

The effect of the combination of rivaroxaban and aspirin compared with aspirin on the primary outcome was consistent in subgroups defined by age, sex, geographic region, body weight, renal function, and history of CV risk factors. The benefits of rivaroxaban and aspirin were evident in patients who were already treated with lipid lowering, blood pressure lowering, and ACE inhibitor therapy, and in those at low, intermediate, and high risk of subsequent CV events. The magnitude of the benefit from rivaroxaban and aspirin appears to be at least comparable to the benefit from other proven secondary prevention therapies such as lipid lowering, blood pressure lowering, and ACE inhibitor therapy, as shown in TABLE 4.

Results in the subgroups with coronary or peripheral artery disease The majority of patients enrolled in COMPASS had CAD (24 824 patients [91%]) and 69% of these patients had

TABLE 3 COMPASS trial results^{8,18,19}

Study group		Rivaroxaban + aspirin, n (%)	Aspirin, n (%)	Rivaroxaban + aspirin versus aspirin	
				HR (95% CI)	P value
Overall group^a					
Efficacy, primary outcome	CV death, stroke, or MI	379 (4.1)	496 (5.4)	0.76 (0.66–0.86)	<0.001
	Ischemic stroke, MI, ALI, or death from CHD	329 (3.6)	450 (4.9)	0.72 (0.63–0.83)	<0.001
	Ischemic stroke, MI, ALI, or CV death	389 (4.3)	516 (5.7)	0.74 (0.65–0.85)	<0.001
	Death from any cause	313 (3.4)	378 (4.1)	0.82 (0.71–0.96)	0.01
Safety	Major bleeding	288 (3.1)	170 (1.9)	1.70 (1.40–2.05)	<0.001
	Fatal bleeding	15 (0.2)	10 (0.1)	1.49 (0.67–3.33)	0.32
	Nonfatal symptomatic ICH	21 (0.2)	19 (0.2)	1.10 (0.59–2.04)	0.77
	Nonfatal, non-ICH, symptomatic bleeding to critical organ	42 (0.5)	29 (0.3)	1.43 (0.89–2.29)	0.14
	Minor bleeding	838 (9.2)	503 (5.5)	1.70 (1.52–1.90)	<0.001
NCB	CV death, stroke, MI, fatal bleeding, or symptomatic bleeding into critical organ	431 (4.7)	534 (5.9)	0.80 (0.70–0.91)	<0.001
CAD group^b					
Efficacy	Primary outcome: MI, stroke or CV death	347 (4.2)	460 (5.6)	0.74 (0.65–0.86)	<0.0001
	MI, ischemic stroke, CHD death, or ALI	299 (3.6)	411 (5.0)	0.72 (0.62–0.83)	<0.0001
	MI, ischemic stroke, CV death, or ALI	349 (4.2)	470 (5.7)	0.73 (0.64–0.84)	<0.0001
	Death	262 (3.2)	339 (4.1)	0.77 (0.65–0.90)	0.0012
Safety	Major bleeding	263 (3.2)	158 (1.9)	1.66 (1.37–2.03)	<0.0001
	Fatal bleeding	14 (0.2)	9 (0.1)	1.55 (0.67–3.58)	0.30
	Nonfatal symptomatic ICH	19 (0.2)	19 (0.2)	0.99 (0.52–1.87)	0.98
	Nonfatal, non-ICH, symptomatic bleeding into critical organ	36 (0.4)	25 (0.3)	1.42 (0.85–2.36)	0.18
NCB	CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ	392 (4.7)	494 (6.0)	0.78 (0.69–0.90)	0.0003
PAD group^c					
Efficacy	Primary outcome: CV death, stroke, MI	126 (5.0)	174 (6.9)	0.72 (0.57–0.90)	0.0047
	CHD death, MI, ischemic stroke, ALI	115 (4.6)	169 (6.7)	0.68 (0.53–0.86)	0.0011
	CV death, MI, ischemic stroke, ALI	142 (5.7)	198 (7.9)	0.71 (0.57–0.88)	0.0019
	Death	129 (5.2)	142 (5.7)	0.91 (0.72–1.16)	–
Safety	Major bleeding	77 (3.1)	48 (1.9)	1.61 (1.12–2.31)	0.0089
	Fatal bleeding	4 (0.2)	3 (0.1)	–	–
	Nonfatal symptomatic ICH	4 (0.2)	8 (0.3)	–	–
	Nonfatal, non-ICH symptomatic bleeding into critical organ	13 (0.5)	8 (0.3)	1.55 (0.64–3.74)	0.33
NCB	CV death, MI, stroke, and critical organ or fatal bleeding	140 (5.6)	185 (7.4)	0.75 (0.60–0.94)	0.011
	CV death, MI, stroke or MALE, major amputation, or fatal or critical organ bleeding	169 (6.8)	234 (9.3)	0.72 (0.59–0.87)	0.0008

a Total number of patients, 27394; patients on rivaroxaban plus aspirin, 9152; patients on aspirin, 9126; **b** Total number of patients, 24824; patients on rivaroxaban plus aspirin, 8313; patients on aspirin, 8261; **c** Total number of patients, 7470; patients on rivaroxaban plus aspirin, 2492; patients on aspirin, 2504

Abbreviations: ALI, acute limb ischemia; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ICH, intracranial hemorrhage; MALE, major adverse limb event; MI, myocardial infarction; NCB, net clinical benefit; others, see TABLE 2

a history of MI. In patients with CAD, treatment with rivaroxaban and aspirin reduced the risk of the primary outcome by 26%, stroke by 44% and mortality by 23%. Major bleeding increased by 66%, but fatal bleeding, nonfatal symptomatic intracranial hemorrhage, or bleeding into a critical organ were not significantly increased.¹⁹ Consistent benefits of rivaroxaban and aspirin treatment were evident irrespective of whether patients were enrolled less than 2 years, 2 to 5 years, or more than 5 years after previous MI and in those without a history of MI.

A post hoc analysis suggested that the additional risk of bleeding in the rivaroxaban and aspirin group, compared with aspirin, decreased over time, whereas the reduction in the primary outcome was constant.

PAD was present in 7470 patients, of whom 3402 (46%) had intermittent claudication and ankle-brachial index (ABI) of more than 0.90, 2045 (27%) had previous revascularization surgery, 4129 (55%) had symptomatic PAD of the lower extremities, and 1919 (26%) had carotid artery disease. Treatment with rivaroxaban and aspirin, compared with aspirin alone, reduced the primary outcome by 28%, increased major bleeding by 61%, and decreased the prespecified limb outcomes of ALI by 44%, MALE by 46%, all vascular amputations by 60%, major amputation by 70%, and MALE plus major amputation by 46%. The reduction in MACE and MALE was consistent in the subgroups with symptomatic PAD, PAD of the lower extremities, and carotid artery disease.

Highest-risk patients The greatest absolute benefit of rivaroxaban and aspirin was seen in patients who were at highest risk of MACE, such as patients with polyvascular disease, and those with diabetes mellitus, heart failure (HF), or chronic kidney disease (CKD).

Polyvascular disease was defined as patients with vascular disease involving more than 1 vascular bed (CAD, PAD, or cerebrovascular disease). The subgroup with polyvascular disease mostly consisted of patients with both CAD and PAD (n = 4906), with a smaller number having both cerebrovascular disease and CAD or both cerebrovascular disease and PAD. Patients with polyvascular disease, compared with those without polyvascular disease, had a higher risk of MACE when treated with aspirin alone (8.5% for 2 major vascular beds and 7.9% for 3 major vascular beds, vs 4.6% for patients without polyvascular disease). Treatment with rivaroxaban and aspirin, compared with aspirin alone, produced a consistent relative risk reduction in MACE, and the absolute risk reduction (ARR) in MACE was higher in patients with polyvascular disease (2.7% for 2 major vascular beds and 3.3% for 3 major vascular beds) than in patients without polyvascular disease (0.8%).

Patients with diabetes mellitus, compared with those without a history of diabetes mellitus, had a high risk of MACE when treated with aspirin alone (6.9% vs 4.6%). Treatment with rivaroxaban and aspirin produced a consistent relative risk reduction in MACE, and the ARR in MACE was higher in patients with diabetes mellitus (1.7%) than in those without diabetes mellitus (1.0%).

HF was defined as the presence of at least 1 sign (dependent edema, increased jugular venous pressure, rales) or 1 symptom (shortness of breath, orthopnea, paroxysmal nocturnal dyspnea), plus either 1 positive diagnostic test (B-type natriuretic peptide >500 pg/ml, or N terminal pro-B-type natriuretic peptide >2000 pg/ml, or chest x-ray showing pulmonary congestion, edema, or pleural effusion) or needing diuretic, nitrate, or inotropic agent to treat the HF. Patients with HF were analyzed because

TABLE 4 Magnitude of the benefits of rivaroxaban and aspirin compared with other proven and widely accepted secondary treatments for cardiovascular prevention

	Proven secondary prevention treatments				Rivaroxaban + aspirin on top of proven secondary prevention treatments
	Lipid lowering by 1 mmol/l ^{20,21}	BP lowering by 10 mm Hg ²²	ACE inhibitors ^{23,24}	β-Blockers ²⁵	Rivaroxaban 2.5 mg bid + aspirin ⁸
MACE	21%	20%	18%	–	24%
Mortality	9%	13%	14%	20%	18%
Stroke	15%	27%	23%	–	42%
MI	24%	17%	18% ^b	25%	14% ^a

Data are presented as relative risk reduction.

a Not statistically significant; b Nonfatal myocardial infarction

Abbreviations: ACE, angiotensin-converting enzyme; bid, twice daily; BP, blood pressure; MACE, major adverse cardiovascular event; others, see TABLE 3

a subgroup analysis of the ATLAS ACS-2 TIMI 51 trial showed that the benefits of rivaroxaban for reduction of MACE were greater in patients with HF than in those without HF.²⁶ Mild or moderate heart failure was present in approximately 5902 (21.5%) COMPASS patients. Patients with HF had a higher risk of MACE than patients without HF when treated with aspirin alone (7.9% vs 4.7%). In this subgroup, treatment with rivaroxaban and aspirin, compared with aspirin alone, produced a consistent relative risk reduction in MACE, and the ARR in MACE was larger in patients with HF (2.4%) than in patients without HF (1.0%). The net clinical benefit of rivaroxaban and aspirin therapy, compared with aspirin, was an ARR of 2.4% in patients with HF, which equates to a number needed to treat of 42.²⁷

Patients with CKD (defined as stage 3 CKD or higher, estimated glomerular filtration rate <60 ml/min), compared with those without CKD, had a higher risk of MACE when treated with aspirin alone (8.4% vs 4.6%). Treatment with rivaroxaban and aspirin, compared with aspirin alone, produced a consistent relative risk reduction in MACE, and the ARR in MACE was larger in patients with CKD (1.9%) than in those without CKD (1.1%).

The larger ARR in MACE with the combination of rivaroxaban and aspirin, compared with aspirin alone, was evident in patients with polyvascular disease, diabetes mellitus, HF, or CKD because these subgroups have a higher baseline risk of MACE than patients without these features.

Graft failure after coronary artery bypass graft

Aspirin reduces the risk of graft failure and MACE in patients who have had a coronary artery bypass graft (CABG), but is only modestly effective. Hypothesizing that the addition of rivaroxaban to aspirin reduces the risk of graft failure and MACE, 1448 patients who had CABG surgery within the previous 4 to 14 days were randomized to the COMPASS trial and had CABG graft patency evaluated with a computed tomography angiogram 1 year after surgery. Triple vessel CAD was present in 77.8% of patients, double vessel disease in 17.1%, and more than 70% of patients underwent on-pump surgery. There was no significant risk reduction in the risk of graft occlusion with aspirin and rivaroxaban (9.1% vs 8.0%; odds ratio [OR], 1.13; 95% CI, 0.82 to 1.57; $P = 0.45$) or rivaroxaban (7.8% vs 8.0%; OR, 0.95; 95% CI, 0.67 to 1.33; $P = 0.75$), compared with aspirin. However, the risk reduction of MACE with rivaroxaban and aspirin compared to aspirin (2.4% vs 3.5%; HR, 0.69; 95% CI, 0.33 to 1.47; $P = 0.34$) was consistent with the risk reduction seen in non-CABG patients. Fatal bleeding or tamponade within 30 days of randomization was not increased

with rivaroxaban and aspirin treatment compared with aspirin treatment.²⁸

How do the results of the COMPASS trial add to prior knowledge?

The results from the COMPASS trial show, for the first time, that long term antithrombotic therapy with the combination of an antiplatelet and an anticoagulant in patients with CAD and PAD produces significant reductions in both morbidity and mortality rates. These benefits were achieved in apparently stable patients already well treated with proven secondary prevention therapies. Previous trials with combinations of aspirin and clopidogrel, ticagrelor, vorapaxar, or warfarin reduced nonfatal CV events at the cost of increased bleeding but did not reduce mortality. The results of COMPASS redefine the concept of residual thrombotic risk, widening it from a mainly lipid mediated definition to vascular/thrombotic risk and provide a significant tool for further reductions of mortality in stable CAD.²⁹

Approval of rivaroxaban 2.5 mg tablets by regulatory authorities

In 2018, the Committee for Medicinal Products for Human Use from the European Medicines Agency, United States Food and Drug Administration, and Health Canada approved the combination of rivaroxaban and aspirin for treatment of patients with stable CAD or PAD.³⁰⁻³² The European Medicines Agency decision is automatically valid and binding for the territories of each European Union member state, including Poland.

Practical implications of COMPASS for countries with high cardiovascular disease burden

In countries like Poland, where the CV disease morbidity and mortality are very high, the benefits of rivaroxaban 2.5 mg twice daily and aspirin treatment for patients and potential cost-effectiveness when taking into account the lifelong risk is likely to be particularly pronounced.²⁹ While the specific pharmacoeconomic analysis for Poland is awaited, the results in high risk patients suggest that the COMPASS treatment strategy may be particularly effective in Poland for patients with stable CAD or PAD. Patients with chronic vascular disease who derive the greatest benefit from the combination of rivaroxaban and aspirin treatment are those with polyvascular disease, mild to moderate HF, CKD, or diabetes mellitus. Such patients had the highest event rates in COMPASS and therefore gain the greatest absolute benefit from the combination of rivaroxaban and aspirin treatment.

A key target population for the COMPASS treatment regimen should include patients with concomitant CAD and PAD who are at particularly high risk. Patients with polyvascular

disease have almost a doubled risk of MACE when compared to patients with disease in a single vascular bed and achieve the greatest ARR in MACE with combination therapy.³³ While a second vascular bed can include carotid atherosclerosis, the results in patients with PAD of the lower extremity are particularly relevant. PAD is highly prevalent in Poland with 30 000 to 40 000 new diagnoses of PAD every year according to Polish National Health Fund data.³⁴ The prevalence of PAD is 3% to 10% in the general population and up to 20% in patients above 65 years of age, whereas asymptomatic PAD is 3- to 4-fold more common. While PAD can be relatively easily diagnosed (for example by means of ABI), this is not routinely performed in patients with atherosclerosis. The results of the COMPASS trial support the noninvasive evaluation of atherosclerosis in other vascular beds, especially PAD of the lower limbs. The lack of effective preventive measures and therapeutic approaches in a pre-COMPASS era has been identified as a primary cause of low popularity of ABI testing in patients with CAD. Late diagnosis of PAD is also associated with limited access to vascular medicine specialists and vascular surgeons in Poland. Many patients reach these reference centers when severe ischemic symptoms have already developed, leading to a high rate of amputation (ranging between 9000–11 000/y) and MALE in PAD patients in Poland. In the light of these facts, the introduction of combination of rivaroxaban 2.5 mg twice daily with aspirin provides an extremely valuable therapeutic option that can be introduced by general physicians and internists.

In whom should the COMPASS treatment be avoided? Rivaroxaban and aspirin treatment should be avoided in patients who cannot tolerate or have a contraindication to aspirin or rivaroxaban, have an unacceptable bleeding risk, or who require long-term dual antiplatelet therapy. Bleeding in patients who take antithrombotic therapy is associated with an increased risk of subsequent CV events.³⁵

Aspirin dose in COMPASS regimen An issue raised in the discussions of COMPASS trial is that aspirin 100 mg once daily was used in combination with rivaroxaban 2.5 mg twice daily. In Poland the typical dose of aspirin used is 75 mg once daily. Considering the pharmacokinetics of aspirin and the results of previous randomized trials evaluating different doses of aspirin, a 75-mg dose of aspirin can be used instead of 100 mg.³⁶

Rivaroxaban: management of bleeding Experience in the COMPASS trial indicates that bleeding that occurs in patients treated with the combination of rivaroxaban 2.5 mg twice

daily and aspirin can be readily managed. Most of the excess bleeds were gastrointestinal, with no significant increase in fatal bleeding, intracranial bleeding, or symptomatic bleeding into a critical organ. Most gastrointestinal bleeds can be managed by interrupting rivaroxaban and aspirin and supportive measures until hemostasis is achieved. Gastrointestinal or genitourinary bleeding that develops in patients who are treated with rivaroxaban and aspirin should prompt investigations for underlying cancer that may have been unmasked by the treatment.

Rivaroxaban: perioperative interruption The time for offset of the anticoagulant effects of rivaroxaban 2.5 mg twice daily is likely shorter than for rivaroxaban 20 mg once daily (because at lower doses rivaroxaban have a shorter half-life) and peak drug levels are much lower. For patients who take rivaroxaban 20 mg daily and have creatinine clearance of 30 ml/min or higher, the last dose of rivaroxaban should be taken no less than 48 hours prior to surgery which has a low bleeding risk, or no less than 72 hours prior surgery which has a high bleeding risk. For patients with creatinine clearance 15 to 29.9 ml/min, the last dose of rivaroxaban should be taken no less than 72 hours prior to surgery which has a low bleeding risk, or no less than 96 hours prior to surgery which has a high bleeding risk.³⁷ A similar approach is reasonable for patients treated with the combination of rivaroxaban 2.5 mg twice daily and aspirin, although it may be overly conservative, as taking the last dose of rivaroxaban 24 hours prior to most types of surgery is likely to provide enough time for the effect of low doses of rivaroxaban to offset, which was tested in COMPASS.

Conclusion The COMPASS trial supports the efficacy of low dose rivaroxaban and aspirin for secondary prevention in patients with stable CAD or PAD. The reduction in MACE, with consistent reductions in the individual components of CV death, stroke, and MI, as well as reductions in MALE and overall mortality have not been previously demonstrated with long-term antithrombotic therapies. Despite an increase in major bleeding with rivaroxaban and aspirin treatment, there is no significant increase in fatal or intracranial bleeding and the net clinical benefit is in favor of rivaroxaban and aspirin treatment. The benefit of rivaroxaban and aspirin treatment appears to be of at least similar magnitude to other proven secondary prevention therapies. The patients with CAD or PAD who will benefit most from this new strategy are those with polyvascular disease, mild or moderate HF, diabetes, or CKD. Clinicians in Poland now have rivaroxaban 2.5 mg tablets available to use in combination with aspirin. This new

strategy has the potential to substantially reduce the risk of MACE, MALE, and mortality in Poland.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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