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Risk factors and clinical outcomes in chronic coronary and peripheral artery disease: An analysis of the randomized, double-blind COMPASS trial

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Abstract

Aims: Secondary prevention in patients with coronary artery disease and peripheral artery disease involves antithrombotic therapy and optimal control of cardiovascular risk factors. In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) study, adding low-dose rivaroxaban on top of aspirin lowered cardiovascular events, but there is limited data about risk factor control in secondary prevention. We studied the association between risk factor status and outcomes, and the impact of risk factor status on the treatment effect of rivaroxaban, in a large contemporary population of patients with coronary artery disease or peripheral artery disease.

Methods and results: We reported ischemic events (cardiovascular death, stroke, or myocardial infarction) in participants from the randomized, double-blind COMPASS study by individual risk factor (blood pressure, smoking status, cholesterol level, presence of diabetes, body mass index, and level of physical activity), and by number of risk factors. We compared rates and hazard ratios of patients treated with rivaroxaban plus aspirin vs aspirin alone within each risk factor category and tested for interaction between risk factor status and antithrombotic regimen. Complete baseline risk factor status was available in 27,117 (99%) patients. Status and number of risk factors were both associated with increased risk of ischemic events. Rates of ischemic events (hazard ratio 2.2; 95% confidence interval 1.8–2.6) and cardiovascular death (hazard ratio 2.0; 1.5–2.7) were more than twofold higher in patients with 4–6 compared with 0–1 risk factors ($p < 0.0001$ for both). Rivaroxaban reduced event rates independently of the number of risk factors (p interaction 0.93), with the largest absolute benefit in patients with the highest number of risk factors.

Conclusion: More favorable risk factor status and low-dose rivaroxaban were independently associated with lower risk of cardiovascular events.

Keywords

Secondary prevention, cholesterol, blood pressure, smoking, physical activity, cardiovascular risk factors, rivaroxaban

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Introduction

Ischemic cardiovascular disease, the most frequent cause of morbidity and mortality across the world, is a combination of progressive atherosclerosis and acute thrombotic complications. Patients with known coronary artery disease (CAD) or peripheral artery disease (PAD) have a high risk of cardiovascular death and disabling vascular events, including stroke, myocardial infarction (MI), and amputations.[1] Secondary prevention in those high-risk patients should be a combination of optimal control of modifiable risk factors to halt the progression of atherosclerosis and of antithrombotic therapies to reduce the occurrence of acute thrombotic events.

The risk factors for atherosclerosis are well-known. Although factors such as genetic predisposition, gender, and age are non-modifiable, many cardiovascular risk factors are modifiable. In primary prevention, modifiable risk factors are the most important predictors of cardiovascular events.[2] Ample evidence supports the control of blood pressure (BP), smoking cessation, prevention and treatment of diabetes, reduction of blood cholesterol levels, reducing obesity, and increasing physical activity in patients with prior events. However, despite the strong recommendations to systematically assess and control modifiable risk factors,[3–5] many patients do not achieve optimal risk factor control,[6] and only a few studies report the effect of the presence of risk factors and their control on clinical outcomes in secondary prevention.

As secondary prevention evolves, novel antithrombotic strategies, lipid-lowering drugs, anti-inflammatory molecules, and novel cardioprotective drugs that reduce blood glucose levels all become options for patients with PAD and/or CAD. With this increase in therapeutic options to target the high residual risk in such patients, physicians and patients may wonder whether traditional preventive measures still remain useful. As prospective interventional studies of the effect of multi-level lifestyle interventions on outcome prove extremely difficult, information about the relation between risk factors on which physicians and patients can act and ischemic outcomes from clinical trials can help to assess the importance of risk factor control in secondary prevention.

In addition to risk factor control, guidelines recommend lifelong single antiplatelet therapy in patients with CAD and/or PAD to reduce the incidence and the impact of acute thrombotic events.[3–5] Recently, the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) study showed that compared with aspirin alone, the addition of rivaroxaban 2.5 mg twice daily (bid) reduced mortality and vascular events but increased the risk of bleeding.[7]

Clinicians who treat CAD and PAD patients face two important clinical questions. First, to what extent is the cardiovascular risk factor status associated with clinical outcomes in those high-risk patients, and second, how does the risk factor status impact the efficacy and safety of antithrombotic therapy.

The COMPASS study represents a large, prospectively followed, well-treated contemporary secondary prevention population. In this analysis, we report the association of baseline risk factor status with outcomes, and evaluate the effect of intensifying antithrombotic therapy according to risk profile.

Methods

Study design and participants

The design and protocol as well as the main results of the COMPASS study have been previously published.[7,8] COMPASS was a multicenter, double-blind, randomized, placebo-controlled trial comparing low-dose rivaroxaban (2.5 mg bid) with aspirin or rivaroxaban alone versus aspirin alone for prevention of cardiovascular death, MI, and stroke in patients with CAD or symptomatic PAD. Detailed definitions of qualifying CAD or PAD have been previously published.[7,8] Importantly, patients with CAD younger than 65 years required atherosclerosis involving at least two vascular beds or at least two additional risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate (GFR) <60 ml per minute, heart failure, or non-lacunar ischemic stroke ≥ 1 month earlier). The main exclusion criteria included severe heart failure with a known ejection fraction of $\leq 30\%$; severe renal insufficiency with a GFR <15 ml/min; a high bleeding risk; a recent ischemic stroke or prior hemorrhagic stroke; use of dual antiplatelet therapy or anticoagulation; or non-cardiovascular conditions deemed by the investigator to be associated with a poor prognosis.

Participants were enrolled from 602 hospitals, clinics, or community practices in 33 countries across six continents. The protocol was approved by health authorities and institutional review boards in all participating countries and written informed consent was obtained from all participants.

Assessment of risk factors

Besides antithrombotic therapy, secondary cardiovascular prevention was left to the discretion of the investigator; no specific cardiovascular risk assessment or risk factor management was specified by the protocol.

At the screening visit, patient demographic information, medical history including presence of diabetes,

smoking status and tobacco use, and medication use were recorded. Validated health and quality of life questionnaires and diet and activity questionnaires were collected at randomization. Baseline measurements of in-office BP, height, and weight were performed, and total cholesterol was measured.

Individual modifiable risk factors and cut-off values

To study the effect of varying degree of control of individual risk factors, we used cut-offs for risk factors based on the available information and on guideline-recommended treatment goals where available. Baseline BP was categorized as optimal control (systolic BP<130 and diastolic BP<85 mm Hg), good control (systolic BP 130–139 and/or diastolic BP 85–89 mm Hg), inadequate control (systolic BP 140–159 and/or diastolic BP 90–99 mm Hg), and uncontrolled (systolic BP≥160 or diastolic BP≥100 mm Hg). Baseline smoking status was categorized as current smoker or nonsmoker, and baseline body mass index (BMI) was calculated from measured height and weight, and categorized as <20, 20–24, 25–29, and ≥30 kg/m^2. As there was no detailed information about the degree of glycemic control, diabetes was categorized as present or absent. We categorized total cholesterol levels (mg/dl) as < 150, 150–249, and ≥250. For physical activity, patients reported weekly time of moderate and vigorous activity during work, for transportation, during leisure-time activities, and as part of household work. From these self-reported data, we calculated minutes of equivalent of moderate physical activity (PA) per week (min-eq/wk) by adding the self-reported weekly time of moderate physical activity (mPA) and double the weekly time of vigorous physical activity (vPA):

$$\mathrm{PA} = \mathrm{mPA} + 2 * \mathrm{vPA}$$

as suggested by the European Society of Cardiology (ESC) secondary prevention guidelines. We used the guideline-recommended cut-offs of < 150 min-eq/wk, 150–299 min-eq/wk, and ≥300 min-eq/wk.

Integrated risk factor control

To evaluate the effect of integrated risk factor status, we classified patients by the number of risk factors at baseline. This was defined as either the presence (for categorical variables) or uncontrolled status (for continuous variables) of each risk factor: systolic BP≥140 or diastolic BP≥90 mm Hg, current smoker, total cholesterol ≥150 mg/dl, presence of diabetes, BMI≥25 or < 20 kg/m^2, and physical activity <150 min-eq/wk. Thus, the number of risk factors ranges from none (optimal risk factor status) to six (least favorable risk factor status). We added a sensitivity analysis using a cut-off for BMI of ≥30 or < 20 kg/m^2.

Outcomes

The primary cardiovascular efficacy outcome was the composite of cardiovascular death, MI, or stroke. Other prespecified efficacy outcomes included PAD outcomes including acute limb ischemia, chronic limb ischemia, and amputation,[9] and the individual components of the primary outcome. A prespecified net clinical benefit outcome was the composite of cardiovascular death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ.

The primary safety outcome was major bleeding defined as the composite of bleeding that was fatal, symptomatic bleeding into a critical organ, surgical site requiring reoperation, or requiring hospitalization (including presentation to an acute care facility without an overnight stay).

Statistical analysis

We present patient baseline demographics and risk factor status by the number of uncontrolled risk factors.

Analyses of the study outcomes were based on the time to a first event and were conducted according to the intention-to-treat principle. Annualized event rates were calculated as number of patients with an outcome per total number of patient-years of follow-up. We used univariate Cox proportional hazards regression models to evaluate risk of study outcomes according to each of the individual risk factors and total number of risk factors: 0–1 (optimal risk factor status), 2, 3, 4, and 5–6. We used stratified Cox proportional hazards models to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the comparison of rivaroxaban plus aspirin vs aspirin alone in subgroups of patients by individual risk factors and total number of risk factors. Significance was tested using stratified log-rank tests. A strata variable was treatment with proton pump inhibitor (PPI) at baseline: not randomized to PPI, randomized to active pantoprazole, randomized to pantoprazole placebo. The assumption of proportional hazards was verified using plots of log of the negative log of survival function against the log of time. Interaction between treatment with rivaroxaban/aspirin and risk factors was tested using stratified Cox models fit to all patients. We used Kaplan-Meier estimates of cumulative hazard to evaluate timing of the study outcomes according to the number of risk factors and treatment with rivaroxaban/aspirin. All reported p values are two-sided. There was no correction for multiple comparisons. Analyses were performed using

SAS software for Linux, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Role of funding source

The COMPASS trial was sponsored by Bayer AG. The sponsor did not influence the analysis plan, drafting of the manuscript or the decision to submit for publication.

Results

Patients demographics and baseline risk factors

Of the 27,395 individuals randomized in COMPASS, 27,117 (99%) had baseline information on BP, total serum cholesterol, smoking status, diabetes status, BMI, and PA. PA questionnaires were unavailable in 205 patients (0.75%). The mean follow-up was 23 months.

Whereas only 743 patients (2.7%) had no uncontrolled risk factors, about half of patients had 0–2 uncontrolled risk factors (49.9%). In 18.6% of patients, more than four risk factors were uncontrolled. Based on the distribution, patients with none and one, and patients with four, five, or six, risk factors were grouped for further analysis to avoid having too small subgroups. Baseline characteristics of patients by number of risk factors are shown in Table 1. Patients with more risk factors were younger, and more likely to have PAD, whereas prior MI and CAD were less frequent in those patients. The use of antihypertensive drugs was more frequent in patients with more risk factors, whereas lipid-lowering treatment at baseline was less frequent in patients with poorer risk factor status.

Cardiovascular events by individual risk factors and by number of risk factors

The primary efficacy event occurred in 1323 participants. Compared with optimal risk factor status, there was a significant and stepwise increase in the rate of ischemic events with poorer control at baseline of each individual risk factor. Compared to optimal control, HRs for individual risk factor status were 1.41 (95% CI 1.19–1.68) for uncontrolled BP, 1.15 (1.01–1.31) for smoking, 1.98 (1.55–2.52) for high serum cholesterol, 1.46 (1.31–1.63) for presence of diabetes, and 1.60 (1.40–1.83) for low levels of PA. For BMI, rates were higher both for low BMI ($<20\,kg/m^2$; HR 1.32, 0.89–1.95) and for high BMI (HR 1.17, 1.00–1.36). Rates of ischemic events increased with the number of risk factors (Figure 1), leading to a 2.2-fold higher risk in patients with four or more risk factors, compared with optimal control (one or no risk factors), for an absolute difference in annual rates of 2% per year (Table 2).

When looking at the components of the primary efficacy outcome, the number of risk factors was strongly related to the occurrence of cardiovascular death, stroke, and MI. Patients with poorest overall risk factor status had a two-fold higher risk of cardiovascular death compared with those with optimal status. Consistent significant stepwise increase in risk for the level of control of each individual risk factor was also seen for the individual outcomes of cardiovascular death, MI, and stroke, although this did not reach significance for blood pressure control and smoking on cardiovascular death, smoking, and BMI for stroke, and smoking for MI (Supplementary Material Table 1).

Uncontrolled BP increased the rate of major bleeding (HR 1.56, 95% CI 1.23–1.96 for uncontrolled vs optimal blood pressure), whereas other risk factors were not associated with rates of major bleeding (Supplementary Material Table 2).

Effect of low-dose rivaroxaban+aspirin vs aspirin alone by cardiovascular risk factors

The COMPASS study has previously reported that the combination of low-dose rivaroxaban and aspirin reduced the risk of major ischemic events by 24% compared to aspirin alone.[7] There was no statistically significant interaction between risk factor status and treatment effect (Table 3), demonstrating the relative risk reduction of rivaroxaban on top of aspirin for each risk factor subgroup (Figure 2). Thus, the rates of ischemic events were lower in patients randomized to the combination of low-dose rivaroxaban and aspirin (9152 patients) compared with those on aspirin alone (9126 patients), regardless of the number of risk factors. Ischemic event rates were lower with more favorable risk factor profile, regardless of the antithrombotic regimen. For the primary efficacy outcome, the absolute reduction in the event rate of rivaroxaban+aspirin as compared with aspirin alone increased with the number of risk factors, from 0.27% per year (number needed to treat (NNT) of 371) in patients with no more than one unfavorable risk factor, to 1.08% per year (NNT of 92) in patients with at least four risk factors (Table 3). Similar findings were found for the individual components of the primary efficacy endpoint (data not shown).

There was no significant interaction between risk factors and antithrombotic treatment assignment with regards to major bleeding (Figure 3). For the net clinical benefit, findings were in line with the overall study results with consistent reductions in the relative risk. However, because the number of risk factors was associated with a larger absolute ischemic risk reduction,

Table 1. Baseline characteristics by integrated risk factor status.

	Number of risk factors			
	0–1 ($n = 5049$)	2 ($n = 8617$)	3 ($n = 8346$)	4–6 ($n = 4006$)
Age (years)	70.1 ± 7.1	69.1 ± 7.5	67.9 ± 8.0	65.5 ± 8.5
Female sex	846 (16.8)	1826 (21.2)	1932 (23.1)	1354 (26.5)
Body mass index (kg/m^2)	25.9 ± 3.9	27.9 ± 4.4	29.0 ± 4.6	30.3 ± 5.0
Systolic blood pressure (mm Hg)	126 ± 13	132 ± 16	140 ± 18	145 ± 17
Diastolic blood pressure (mm Hg)	74 ± 8	76 ± 9	79 ± 10	82 ± 10
Total cholesterol (mg/dl)	137.8 ± 29.6	155.6 ± 38.8	169.2 ± 40.8	182.4 ± 41.8
Current smoker	195 (3.9)	1081 (12.5)	2015 (24.1)	2521 (49.4)
Hypertension	3299 (65.3)	6282 (72.9)	6573 (78.8)	4260 (83.4)
Diabetes	343 (6.8)	2169 (25.2)	3775 (45.2)	3935 (77.1)
Physical activity (min-eq/wk)	1695 ± 2504	1610 ± 2344	1494 ± 2234	1177 ± 2400
Previous stroke	133 (2.6)	295 (3.4)	310 (3.7)	279 (5.5)
Previous myocardial infarction	3265 (64.7)	5523 (64.1)	5097 (61.1)	2990 (58.6)
Heart failure	791 (15.7)	1789 (20.8)	1981 (23.7)	1265 (24.8)
Coronary artery disease	4814 (95.3)	7995 (92.8)	7489 (89.7)	4264 (83.5)
Peripheral artery disease	914 (18.1)	2044 (23.7)	2470 (29.6)	1967 (38.5)
Estimated GFR				
<30 ml/min	32 (0.6)	56 (0.6)	80 (1.0)	71 (1.4)
30 to <60 ml/min	1015 (20.1)	1926 (22.4)	1867 (22.4)	1164 (22.8)
≥ 60 ml/min	4002 (79.3)	6635 (77.0)	6397 (76.7)	3870 (75.8)
Race				
White	3175 (62.9)	5607 (65.1)	5307 (63.6)	2788 (54.6)
Black	32 (0.6)	76 (0.9)	63 (0.8)	87 (1.7)
Asian	1024 (20.3)	1321 (15.3)	1192 (14.3)	681 (13.3)
Other	818 (16.2)	1613 (18.7)	1784 (21.4)	1549 (30.3)
Geographic region				
North America	977 (19.4)	1334 (15.5)	1030 (12.3)	530 (10.4)
South America	830 (16.4)	1708 (19.8)	1924 (23.1)	1609 (31.5)
Western Europe, Israel, Australia, or South Africa	1697 (33.6)	2855 (33.1)	2614 (31.3)	1327 (26.0)
Eastern Europe	601 (11.9)	1493 (17.3)	1673 (20.0)	1006 (19.7)
Asia-Pacific	944 (18.7)	1227 (14.2)	1105 (13.2)	633 (12.4)
Medication				
ACE inhibitor or ARB	3382 (67.0)	6062 (70.3)	6082 (72.9)	3801 (74.5)
Calcium-channel blocker	1123 (22.2)	2205 (25.6)	2298 (27.5)	1580 (31.0)
Diuretic	1107 (21.9)	2454 (28.5)	2684 (32.2)	1780 (34.9)
Beta blocker	3526 (69.8)	6071 (70.5)	5904 (70.7)	3473 (68.0)
Lipid-lowering agent	4763 (94.3)	7902 (91.7)	7422 (88.9)	4277 (83.8)
NSAID	211 (4.2)	434 (5.0)	469 (5.6)	337 (6.6)
Non-study PPI	1854 (36.7)	3127 (36.3)	2961 (35.5)	1757 (34.4)

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; GFR: glomerular filtration rate; NSAID: non-steroidal antiflogistic drug; PPI: proton pump inhibitor.

Number of risk factors: (+1) if baseline systolic blood pressure $\geq$140 mm Hg or diastolic blood pressure $\geq$90 mm Hg; (+1) if current smoker; (+1) if baseline total cholesterol $\geq$150 mg/dl; (+1) presence of diabetes; (+1) if baseline body mass index <20 kg/m^2 or ≥ 25 kg/m^2; (+1) if physical activity <150 min-eq/wk. For continuous variables, plus-minus values are mean ± standard deviation. For categorical variables, frequency (percentage) are shown. Values of p were <0.0001 for all variables, except non-study PPI use $p = 0.25$.

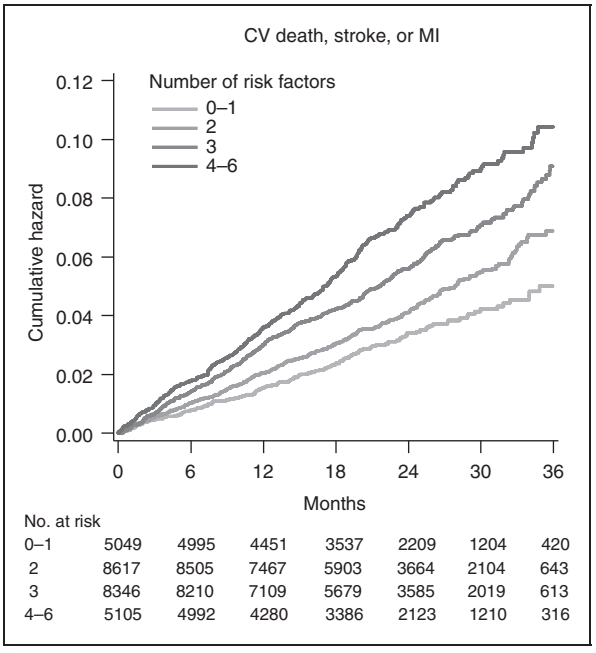

Figure 1. Incidence rates of the primary efficacy outcome by the number of risk factors.
Number of risk factors refers to presence of diabetes; current smoker; poor baseline control of blood pressure; lowest level of physical activity at baseline; lowest or highest level of body mass index (BMI) at baseline; and highest level of total cholesterol at baseline. CV: cardiovascular.

without affecting the risk of major bleeding, the absolute effect on net clinical benefit of rivaroxaban-plus-aspirin was larger in patients with more cardiovascular risk factors: 1.05% per year absolute risk reduction in patients with four to six risk factors (NNT of 96), vs 0.31% per year absolute risk reduction in patients with none or one risk factor (NNT of 319) (Table 4 and Figure 3).

Risk factor status and treatment effect in patients with PAD vs CAD

Overall, rates of CV death, stroke, MI, or major adverse limb events were higher in the subgroup of patients with PAD with or without CAD than in patients with CAD alone. In PAD patients, the rate of ischemic events increased with the number of risk factors. Within each risk factor category, the effect of rivaroxaban on top of aspirin was conserved (Figure 4).

Discussion

This analysis examines the effects of risk factor status and antithrombotic therapy on cardiovascular events in CAD and PAD patients in the COMPASS study, a large, well-controlled, contemporary secondary cardiovascular prevention population. Our analyses demonstrate that cardiovascular risk factor status and antithrombotic therapy have an independent and additive effect on cardiovascular outcomes in these high-risk patients.

Recent pivotal studies in secondary prevention have focused on adding novel pharmacological strategies, such as intensifying antithrombotic therapy,[7,10,11] lowering lipid levels,[12,13] improving glycemic control,[14] and addressing inflammation,[15] to reduce the high residual risk. Although some of these strategies have shown to improve outcomes, they add costs and potential adverse events. Despite the strong evidence on the importance of risk factors in primary prevention, there is a lack of robust data showing whether the status of potentially modifiable risk factors still affects outcomes in patients who are at very high risk, and who receive state-of-the-art secondary prevention therapy.

Our analysis encourages the physician to increase further efforts to control modifiable risk factors. Indeed, for each individual risk factor for which we had continuous data, better control was associated with a lower rate of cardiovascular events. Furthermore, the number of unfavorable risk factors (either presence or poorly controlled status at baseline) was strongly associated with cardiovascular events. Compared with four or more risk factors, patients with optimal risk factor status had a two-fold lower risk of fatal or non-fatal events, or an absolute difference of 2%/year.

We did not find an interaction between risk factor status and the treatment effect of rivaroxaban. Compared with aspirin alone, the addition of rivaroxaban was associated with a consistent relative reduction in ischemic events irrespective of the risk factor profile. However, absolute risk reduction increased as patients had more risk factors and a higher absolute risk of events. Uncontrolled BP was associated with higher rates of major bleeding, but status of other risk factors did not affect bleeding risk. As a result, the absolute reduction in the net clinical outcome increased with the number of risk factors.

This analysis shows that a large proportion of high-risk patients, treated by specialists, are not optimally controlled, confirming observational data in secondary prevention.[6,16] There may be many reasons for this, including access to therapies, the perceived importance of risk factor control, a lack of structured approaches for life-style management, and difficulty attaining control (e.g. due to drug adverse events or intolerance). The current study gives some indirect insight into underlying reasons for suboptimal control. A large proportion (70%) of patients with optimal BP control had a history of hypertension, reflecting adequate treatment. On the other hand, patients with poor BP control

Table 2. Rates of the primary efficacy outcome according to individual risk factors in the overall study population ($n = 27,395$).

	Primary efficacy outcome: CV death, stroke, or myocardial infarction			
	No. of first events/ patients (%)	Annual rate, %/year	Hazard ratio (95% CI)	*p* Value
Blood pressure control				0.0006
Optimal	431/9755 (4.4)	2.4	*Ref. group*	
Good	275/6201 (4.4)	2.4	1.00 (0.86–1.17)	
Inadequate	438/8627 (5.1)	2.6	1.12 (0.98–1.28)	
Uncontrolled	179/2810 (6.4)	3.3	1.41 (1.19–1.68)	
Smoking				0.03
No current smoker	1020/21,528 (4.7)	2.5	*Ref. group*	
Current smoker	303/5867 (5.2)	2.8	1.15 (1.01–1.31)	
Total cholesterol				<0.0001
<150 mg/dl	494/11,601 (4.3)	2.2	*Ref. group*	
150 to <250 mg/dl	754/14,776 (5.1)	2.7	1.21 (1.08–1.35)	
≥250 mg/dl	75/962 (7.8)	4.4	1.98 (1.55–2.52)	
Diabetes				<0.0001
No	706/17,054 (4.1)	2.2	*Ref. group*	
Yes	617/10,341 (6.0)	3.2	1.46 (1.31–1.63)	
Body mass index				0.19
<20 kg/m^2	28/496 (5.6)	3.0	1.32 (0.89–1.95)	
20 to <25 kg/m^2	266/6129 (4.3)	2.3	*Ref. group*	
25 to <30 kg/m^2	576/12,047 (4.8)	2.5	1.10 (0.95–1.27)	
≥30 kg/m^2	445/8701 (5.1)	2.7	1.17 (1.00–1.36)	
Physical activity				<0.0001
≥300 min-eq/wk	905/20,506 (4.4)	2.3	*Ref. group*	
150 to <300 min-eq/wk	130/2552 (5.1)	2.7	1.16 (0.96–1.39)	
<150 min-eq/wk	278/4132 (6.7)	3.7	1.60 (1.40–1.83)	
Number of risk factors				<0.0001
0–1	160/5049 (3.2)	1.6	*Ref. group*	
2	350/8617 (4.1)	2.1	1.30 (1.08–1.56)	
3	454/8346 (5.4)	2.9	1.75 (1.46–2.09)	
4–6	341/5105 (6.7)	3.6	2.19 (1.81–2.64)	

CI: confidence interval; CV: cardiovascular.

Percentage (%) is the proportion of patients with an outcome. Percentage per year (%/year) is the rate per 100 patient-years of follow-up. Hazard ratios (95% CI) and *p* values are from the univariate Cox proportional hazards regression models.

had higher baseline numbers of antihypertensive drugs, suggesting that inadequate BP control is often due to ''resistant'' patients rather than lack of treatment. In contrast, patients with poor control of cholesterol had a lower use of lipid-lowering drugs.

Important strengths of this study include the very large contemporary population of well-characterized CAD and PAD patients with rigorous prospective follow-up in the setting of a randomized clinical trial. Importantly, baseline information was available on (aspects of) six modifiable risk factors, including PA.

There are limitations to be acknowledged. First, this study is a non-prespecified subanalysis within a randomized controlled trial, rather than a randomized comparison of an intervention to improve risk factor control. Therefore, importantly, while this study clearly shows an association between (un)controlled risk factors and cardiovascular events, our analysis cannot formally assess the effect of an intervention to improve risk factors on outcomes. Patients with poor risk factor control may have been exposed to those risk factors for a long time, and actively reducing them may not yield the same magnitude of effect as not having been exposed to the risk factor at all. Furthermore, patients in whom it is difficult to control risk factors may represent a more severely ill population, though

Table 3. Antithrombotic treatments and risk of the primary efficacy outcome by category of risk factor status.

	Rivaroxaban plus aspirin ($n = 9152$)		Aspirin alone ($n = 9126$)		Rivaroxaban plus aspirin vs aspirin alone		
	No. of first events/ patients (%)	Annual rate, %/year	No. of first events/ patients (%)	Annual rate, %/year	Hazard ratio (95% CI)	*p* Value	*p* Value for interaction
Primary efficacy outcome: CV death, stroke, or myocardial infarction							
Blood pressure control							0.84
Optimal	121/3256 (3.7)	2.0	156/3250 (4.8)	2.6	0.77 (0.61–0.97)	0.03	
Good	79/2033 (3.9)	2.1	104/2117 (4.9)	2.6	0.79 (0.59–1.06)	0.12	
Inadequate	126/2942 (4.3)	2.2	171/2821 (6.1)	3.2	0.69 (0.55–0.87)	0.002	
Uncontrolled	53/920 (5.8)	3.0	65/937 (6.9)	3.7	0.81 (0.56–1.17)	0.26	
Smoking							0.29
No current smoker	299/7208 (4.1)	2.2	374/7154 (5.2)	2.7	0.79 (0.68–0.92)	0.002	
Current smoker	80/1944 (4.1)	2.3	122/1972 (6.2)	3.4	0.66 (0.50–0.88)	0.004	
Total cholesterol							0.54
<150 mg/dl	138/3915 (3.5)	1.8	174/3824 (4.6)	2.4	0.76 (0.61–0.95)	0.02	
150 to <250 mg/dl	225/4895 (4.6)	2.4	293/4982 (5.9)	3.1	0.78 (0.65–0.92)	0.004	
≥ 250 mg/dl	16/317 (5.0)	2.9	29/308 (9.4)	5.3	0.55 (0.30–1.02)	0.05	
Diabetes							0.77
No	200/5704 (3.5)	1.8	257/5652 (4.5)	2.4	0.77 (0.64–0.93)	0.005	
Yes	179/3448 (5.2)	2.7	239/3474 (6.9)	3.7	0.74 (0.61–0.90)	0.002	
Body mass index							0.22
<20 kg/m^2	12/179 (6.7)	3.6	8/163 (4.9)	2.8	1.35 (0.55–3.30)	0.51	
20 to <25 kg/m^2	69/2044 (3.4)	1.8	105/2068 (5.1)	2.7	0.66 (0.49–0.90)	0.007	
25 to <30 kg/m^2	173/4045 (4.3)	2.3	199/3926 (5.1)	2.7	0.85 (0.69–1.04)	0.11	
≥ 30 kg/m^2	120/2872 (4.2)	2.2	181/2963 (6.1)	3.2	0.66 (0.53–0.84)	0.0005	
Physical activity							0.79
≥ 300 min-eq/wk	255/6837 (3.7)	1.9	348/6825 (5.1)	2.7	0.73 (0.62–0.86)	0.0001	
150 to <300 min-eq/wk	34/835 (4.1)	2.1	47/861 (5.5)	2.9	0.72 (0.46–1.12)	0.15	
<150 min-eq/wk	84/1402 (6.0)	3.3	100/1381 (7.2)	4.0	0.81 (0.61–1.09)	0.16	
Number of risk factors							0.86
0–1	48/1718 (2.8)	1.4	55/1680 (3.3)	1.7	0.84 (0.57–1.24)	0.39	
2	87/2826 (3.1)	1.6	132/2904 (4.5)	2.4	0.68 (0.52–0.89)	0.005	
3	133/2787 (4.8)	2.5	171/2730 (6.3)	3.3	0.75 (0.60–0.94)	0.01	
4–6	100/1709 (5.9)	3.1	134/1735 (7.7)	4.2	0.74 (0.57–0.96)	0.02	

CI: confidence interval; CV: cardiovascular.
Percentage (%) is the proportion of patients with an outcome. Percentage per year (%/year) is the rate per 100 patient-years of follow-up.
Hazard ratios (95% CI) are from the stratified Cox proportional hazards regression models. Values of *p* are from the stratified log-rank tests.

the lack of a relationship with bleeding argues against this. Nevertheless, the consistent finding of the strong relationship between poor control and ischemic events provides compelling arguments for the importance of risk factor control.

Due to study design, there were some limitations in the availability of data. Risk factor control was only based on baseline data, and not on dynamic assessment during follow-up. We could, therefore, not assess the effect of changes in risk factors throughout the trial. However, if risk factor control would improve during the trial duration, our analysis would under-, rather than overestimate the effect or risk factors. Furthermore, as we did not have data on glycemic control, we used the presence or absence of diabetes.

The assessment of risk factor control in clinical practice is often a trade-off between precision and practical issues. For BP, although automated and ambulatory BP measurement methods are more closely linked to cardiovascular outcomes, in-office measurement is still the predominant assessment of BP control during patient follow-up. Similarly, BMI is only a rough

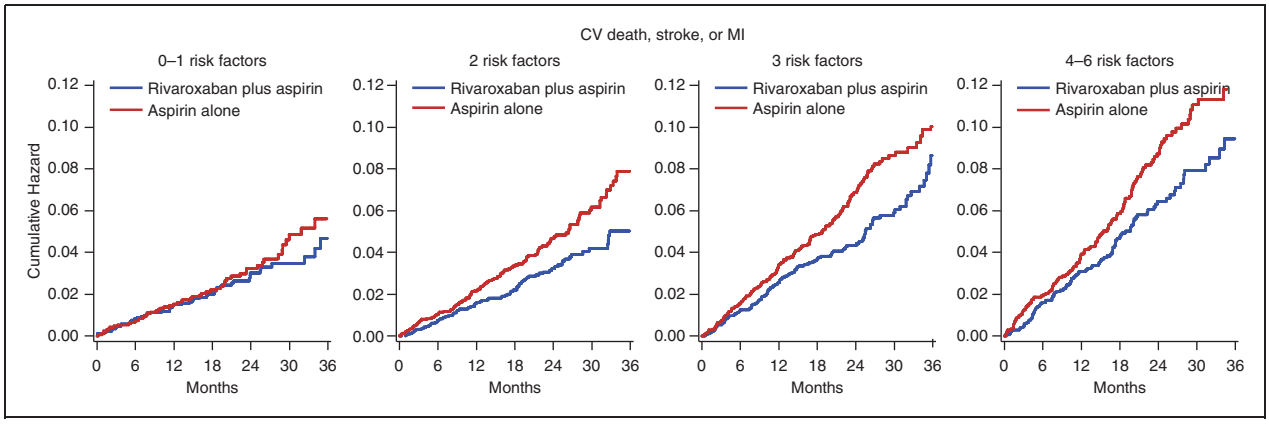

Figure 2. Incidence rates of the primary efficacy outcome by the number of risk factors and antithrombotic treatment group. Number of risk factors refers to presence of diabetes; current smoker; poor baseline control of blood pressure; lowest level of physical activity at baseline; lowest or highest level of body mass index (BMI) at baseline; and highest level of total cholesterol at baseline. CV: cardiovascular; MI: myocardial infarction.

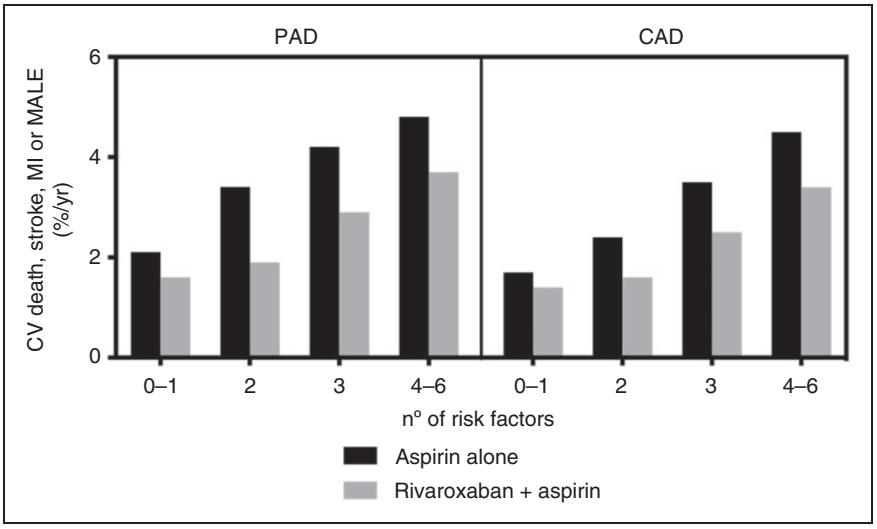

Figure 3. Efficacy, safety, and net clinical benefit of antithrombotic therapy by baseline risk factor status. CV: cardiovascular; MI: myocardial infarction.

marker for adiposity compared waist-to-hip ratio or to more robust but impractical direct measurements. Finally, evaluation of physical activity is typically based on self-reported data, rather than direct measurements. As data collection in COMPASS represented clinical reality, we acknowledge that a more elaborate evaluation of each risk factor may further improve the quality of the reported association. However, even with the current measurements, we found clear and consistent associations between risk factor status and outcomes.

In choosing cut-off values for risk factor categorization, we used guideline-recommended values where available to define optimal vs less optimal values for individual risk factors. To ensure maximal clinical relevance and to avoid overstating the effect of risk factors by singling out only the most extreme categories of risk factors, we chose to count patients with less than optimal risk factors, rather than those that were extremely uncontrolled. As shown in Table 2, the effect of individual risk factors is stronger for more extreme values. Choosing a higher cut-off for BMI (and BMI, cholesterol, etc.) would therefore amplify the relation between baseline risk factor status and outcomes. Our findings of a clear and linear relationship between the number of risk factors with less than optimal status and cardiovascular outcomes becomes even more compelling using these conservative categories. A sensitivity analysis using a more conservative cut-off for BMI did not affect our findings (data not shown).

Table 4. Antithrombotic treatments and risk of major bleeding and net clinical benefit by category of risk factor status.

	Rivaroxaban plus aspirin ($n = 9152$)		Aspirin alone ($n = 9126$)		Rivaroxaban plus aspirin vs aspirin alone		
	No. of first events/ patients (%)	Annual rate, %/year	No. of first events/ patients (%)	Annual rate, %/year	Hazard ratio (95% CI)	*p* Value	*p* Value for interaction
Major bleeding							
Blood pressure control							0.89
Optimal	87/3256 (2.7)	1.4	57/3250 (1.8)	0.9	1.52 (1.09–2.13)	0.01	
Good	56 /2033 (2.8)	1.5	34/2117 (1.6)	0.9	1.74 (1.13–2.66)	0.01	
Inadequate	101/2942 (3.4)	1.8	55/2821 (1.9)	1.0	1.77 (1.27–2.46)	0.0006	
Uncontrolled	44/920 (4.8)	2.5	24/937 (2.6)	1.3	1.87 (1.14–3.08)	0.01	
Smoking							0.46
No current smoker	227/7208 (3.1)	1.6	138/7154 (1.9)	1.0	1.64 (1.33–2.02)	<0.0001	
Current smoker	61/1944 (3.1)	1.7	32/1972 (1.6)	0.9	1.97 (1.28–3.02)	0.002	
Total cholesterol							0.12
<150 mg/dl	127/3915 (3.2)	1.7	72/3824 (1.9)	1.0	1.73 (1.29–2.31)	0.0002	
150 to < 250 mg/dl	157/4895 (3.2)	1.7	91/4982 (1.8)	1.0	1.77 (1.37–2.29)	<0.0001	
≥250 mg/dl	3/317 (0.9)	0.5	7/308 (2.3)	1.2	0.44 (0.11–1.70)	0.22	
Diabetes							0.97
No	178/5704 (3.1)	1.6	105/5652 (1.9)	1.0	1.69 (1.33–2.15)	<0.0001	
Yes	110/3448 (3.2)	1.7	65/3474 (1.9)	1.0	1.70 (1.25–2.31)	0.0006	
Body mass index							0.32
<20 kg/m^2	8/179 (4.5)	2.4	3/163 (1.8)	1.0	2.29 (0.61–8.64)	0.21	
20 to < 25 kg/m^2	60/2044 (2.9)	1.6	43/2068 (2.1)	1.1	1.43 (0.96–2.11)	0.07	
25 to < 30 kg/m^2	129/4045 (3.2)	1.7	61/3926 (1.6)	0.8	2.08 (1.53–2.82)	<0.0001	
≥30 kg/m^2	91/2872 (3.2)	1.6	63/2963 (2.1)	1.1	1.47 (1.07–2.03)	0.02	
Physical activity							0.50
≥300 min-eq/wk	209/6837 (3.1)	1.6	120/6825 (1.8)	0.9	1.76 (1.40–2.20)	<0.0001	
150 to < 300 min-eq/wk	27/835 (3.2)	1.7	22/861 (2.6)	1.4	1.21 (0.69–2.13)	0.51	
<150 min-eq/wk	47/1402 (3.4)	1.8	28/1381 (2.0)	1.1	1.66 (1.04–2.64)	0.03	
Number of risk factors							0.42
0–1	40/1718 (2.3)	1.2	31/1680 (1.8)	1.0	1.25 (0.78–2.00)	0.34	
2	90/2826 (3.2)	1.7	56/2904 (1.9)	1.0	1.69 (1.21–2.36)	0.002	
3	99/2787 (3.6)	1.9	48/2730 (1.8)	0.9	2.04 (1.45–2.88)	<0.0001	
4–6	54/1709 (3.2)	1.7	35/1735 (2.0)	1.1	1.57 (1.03–2.40)	0.04	
Net clinical benefit: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ							
Number of risk factors							0.93
0–1	56/1718 (3.3)	1.7	64/1680 (3.8)	2.0	0.85 (0.59–1.21)	0.36	
2	104/2826 (3.7)	1.9	145/2904 (5.0)	2.6	0.74 (0.58–0.96)	0.02	
3	150/2787 (5.4)	2.8	178/2730 (6.5)	3.5	0.81 (0.65–1.01)	0.06	
4–6	110/1709 (6.4)	3.5	143/1735 (8.2)	4.5	0.76 (0.60–0.98)	0.03	

CI: confidence interval; CV: cardiovascular.

Percentage (%) is the proportion of patients with an outcome. Percentage per year (%/year) is the rate per 100 patient-years of follow-up. Hazard ratios (95% CI) are from the stratified Cox proportional hazards regression models. Values of *p* are from the stratified log-rank tests.

In conclusion, this analysis supports the importance of both control of cardiovascular risk factors and optimal antithrombotic therapy to achieve optimal (cardio)vascular protection. Nevertheless, only a small proportion of secondary prevention patients achieve optimal risk factor status. The implications of this study are threefold.

First, patients with fewer risk factors and who achieve better control of individual risk factors have a

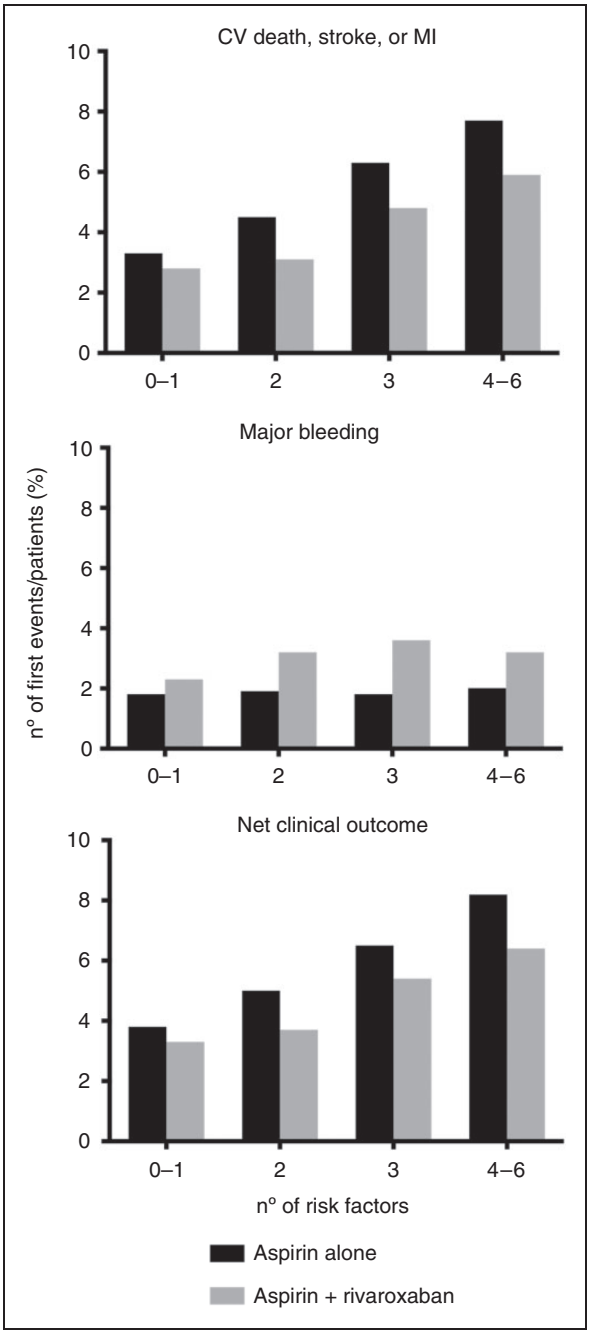

Figure 4. Effect of antithrombotic therapy and risk factor status in peripheral artery disease (PAD) and coronary artery disease (CAD) patients.
CV: cardiovascular; MI: myocardial infarction.

significantly better outcome. The magnitude of the effect of risk factor status provides strong encouragement for physicians and policy makers to improve risk factor control overall, whereas the integrated effect implies that if control of an individual risk factor is difficult or impossible to achieve (e.g. unwillingness to stop smoking, therapy-resistant hypertension, etc.), patients may still benefit from controlling other risk factors.

Second, in addition to aspirin, rivaroxaban provides an additional reduction in vascular events that is independent from the status of risk factors. The relative risk reduction offered by rivaroxaban is consistent across all groups, resulting in a higher absolute risk reduction in patients with more unfavorable risk factor status.

Finally, the effect of risk factor status and more intense antithrombotic therapy is independent. Therefore, optimal vascular protection integrates optimal control of modifiable risk factors and antithrombotic therapy.

Author contribution

TV, PV, JB, SSA, and JWE contributed to the conception and design of the work. TV, PV, and OS contributed to the acquisition and analysis of data, and TV, PV, JB, SSA, and JWE contributed to the interpretation of data for the work. The manuscript was drafted by TV. All authors critically revised the manuscript and provided input on the interpretation, formulation, and presentation of the data, as well as on the discussion. All authors gave approval for the final manuscript.

Declaration of conflicting interests

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