Low-dose rivaroxaban plus aspirin in patients with polypharmacy and multimorbidity: an analysis from the COMPASS trial

Authors:

Thomas Vanassche[1], Peter Verhamme[1], Sonia S. Anand[2], Olga Shestakovska[2], Darryl P. Leong[2], Keith A.A. Fox[3], Deepak L. Bhatt[4], Alvaro Avezum[5], Marco Alings[6], Victor Aboyans[7], Aldo P. Maggioni[8], Petr Widimsky[9], Eva Muehlhofer[10], Scott D. Berkowitz[11], Salim Yusuf[2], Stuart J. Connolly[2], John W. Eikelboom[2], and Jackie Bosch[2]

Affiliations:

[1] University Hospitals Leuven, Dept. of Cardiovascular Sciences, Leuven, Belgium

[2] Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada

[3] Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom

[4] Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, United States

[5] International Research Center, Hospital Alemão Oswaldo Cruz, São Paulo, Brasil

[6] Amphia Ziekenhuis and Werkgroep Cardiologische Centra Nederland, Utrecht, the Netherlands

[7] Dept. of Cardiology, Dupuytren University Hospital, and INSERM 1094 & IRD, Limoges University, Limoges, France

[8] Associazione Nazionale Medici Cardiologi Ospedalieri Research Center, Florence, Italy

[9] Cardiocenter, University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic

[10] Bayer AG, Wuppertal, Germany

[11] Bayer U.S. LLC, Whipanny, US

Corresponding author:

Thomas Vanassche, M.D. PhD

Department of Cardiovascular Sciences

University Hospitals Leuven, KULeuven

Herestraat 49

B-3000 Leuven

Belgium

Phone +32 16 34 34 91

Fax +32 16 34 34 94

Email thomas.vanassche@uzleuven.be

Abstract

Background

In patients with coronary or peripheral arterial disease, adding low dose rivaroxaban to aspirin reduces cardiovascular events and mortality. Polypharmacy and multimorbidity are frequent in such patients.

Aims

To analyze whether the benefits and risks of rivaroxaban plus aspirin varies in patients with comorbidities and receiving multiple drugs.

Methods and results

We describe ischemic events (cardiovascular death, stroke, or myocardial infarction) and major bleeding in participants from the randomised, double-blind COMPASS study by number of cardiovascular medications and concomitant medical conditions. We compared event rates and hazard ratios (HR) for rivaroxaban plus aspirin versus aspirin alone by the number of medications and concomitant conditions, and tested for interaction between polypharmacy or multimorbidity and the antithrombotic regimen.

The risk of ischemic events was higher in patients with more concomitant drugs (HR 1.7, 95%CI 1.5-2.1 for >4 vs 0-2) and with more comorbidities (HR 2.3, 1.8-2.1 for >3 vs 0-1). Multimorbidity, but not polypharmacy, was associated with a higher risk of major bleeding. The relative efficacy, safety, and net clinical benefit of rivaroxaban were not affected by the number of drugs or comorbidities. Patients taking more concomitant medications derived the largest absolute reduction in the net clinical outcome with added rivaroxaban (1.1% vs 0.4% reduction with >4 vs 0-2 cardiovascular drugs, NNT 91 vs 250).

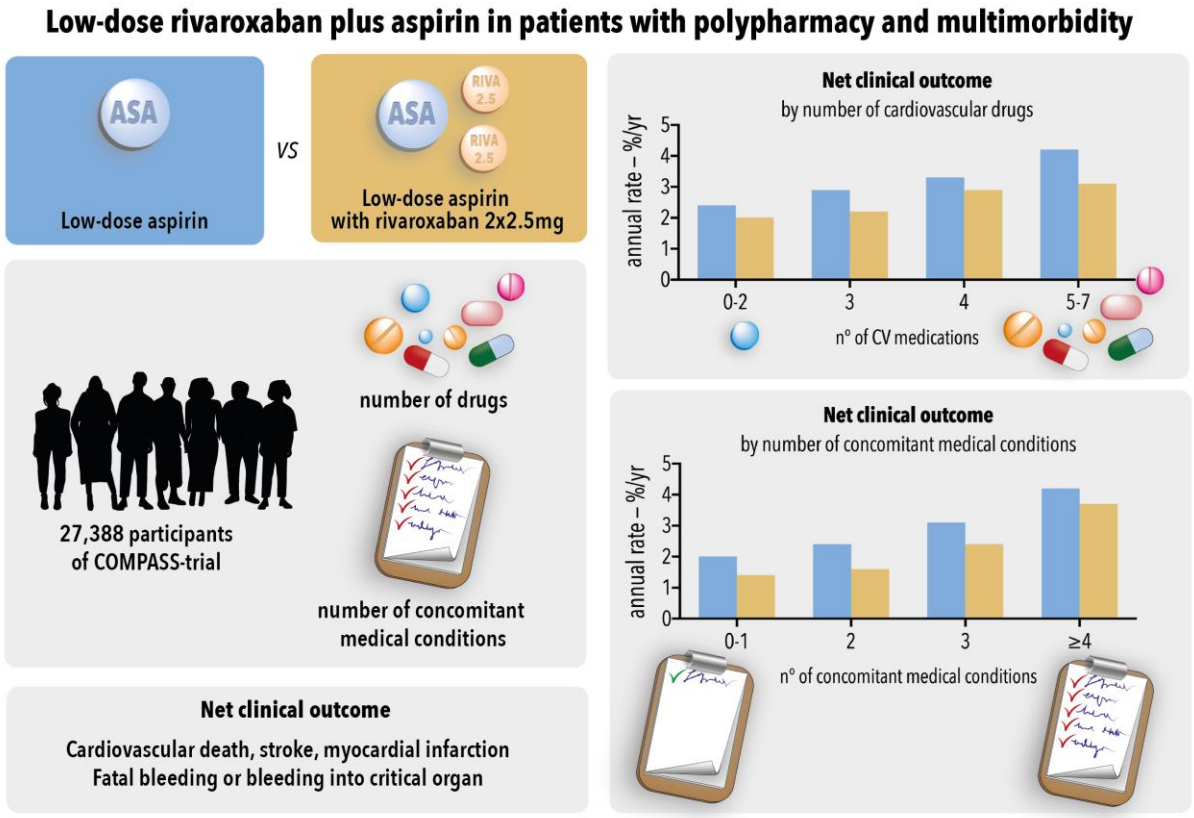
Conclusion

Adding low-dose rivaroxaban to aspirin resulted in benefits irrespective of the number of concomitant drugs or comorbidities. Multiple comorbidities and/or polypharmacy should not dissuade the addition of rivaroxaban to aspirin in otherwise eligible patients.

Keywords:

Chronic coronary syndrome, rivaroxaban, prevention, polypharmacy, multimorbidity

Graphical abstract



Introduction

The burden of cardiovascular disease remains high despite important advances in prevention and treatment. Many pharmacological therapies reduce events in patients with known cardiovascular disease, including lipid-lowering, antihypertensive, antidiabetic and antithrombotic drugs, and guideline-recommended targets for low-density lipoprotein cholesterol, blood pressure and HbA1C are increasingly rigorous[1-3]. As a result, patients with known cardiovascular disease often require several drugs to reach these targets.

Furthermore, because risk factors for atherosclerosis (such as smoking, obesity, hypercholesteremia, hypertension and diabetes) also predispose to other medical conditions, patients with cardiovascular disease often have concomitant medical conditions, which may in turn necessitate additional pharmacotherapy[4]. Multimorbidity is also a marker of frailty[5].

The COMPASS study demonstrated that the combination of aspirin 100 mg once-daily with rivaroxaban 2.5mg twice-daily reduced major cardiovascular events and cardiovascular mortality compared to aspirin alone, with an increase in major bleedings[6]. Based on this finding, the most recent guidelines for patients with chronic coronary syndromes recommend adding low-dose rivaroxaban (IIa recommendation) in patients with high risk of recurrent events, and considering low-dose rivaroxaban (IIb recommendation) in patients even at moderate risk of ischemic events, provided that bleeding risk is low[1].

Polypharmacy and multimorbidity are often considered barriers to add evidence-based therapies, especially when they include a bleeding risk[7, 8]. Physicians and patients may be

more reluctant to add drugs in patients who are already taking several pills or who have many comorbidities[9], due to concern about the number of pills, about potential drug-drug interactions and adverse events, and uncertainty whether the reported efficacy and safety remain consistent in patients with polypharmacy and multimorbidity.

In this paper, we describe whether the efficacy and safety outcomes of intensified antithrombotic therapy are affected by the concomitant intake of common cardiovascular drug classes. We also investigated if the total number of concomitant cardiovascular drugs and of overall drugs impacted on the efficacy (reduction in ischemic events) and safety outcomes (bleeding events) of participants in the COMPASS trial. Finally, we explored the effects of dual pathway inhibition on outcomes in patients based on the number of comorbidities.

Methods

Trial participants and study design

This is a post-hoc subgroup analysis of the COMPASS study, a multicentre, double-blind, randomized placebo-controlled trial, compared aspirin alone, low-dose rivaroxaban with aspirin, or rivaroxaban alone in patients with stable vascular disease. Additionally, patients who were not treated with a proton pump inhibitor (PPI) at baseline were randomized to study PPI or placebo. The COMPASS design[10] and main results[6] have been published. In short, COMPASS participants had CAD and/or PAD without requirements for therapeutic anticoagulation or dual antiplatelet therapy. Patients with CAD under 65 years required either at least two affected vascular beds, or at least two additional cardiovascular risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [GFR] <60

ml per minute, heart failure, or prior non-lacunar ischemic stroke). Main exclusion criteria included heart failure with a known ejection fraction of ≤30%; severe renal insufficiency (GFR <15ml/min), liver disease associated with coagulopathy, an ischemic stroke less than one month prior to inclusion or any prior haemorrhagic stroke, a high bleeding risk, or non-cardiovascular conditions deemed by the investigator to be associated with a poor prognosis.

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

Demographic information

At the screening visit, patient demographic information and medical history were collected, baseline measurements of in-office blood pressure, height, and weight were performed, and serum creatinine and total cholesterol were measured. Validated health and quality of life questionnaires and diet and activity questionnaires were collected at randomization.

Polypharmacy

At the randomization visit, baseline use of drugs for cardiovascular conditions or cardiovascular prevention was collected. This included lipid-lowering agents, beta blockers, calcium-channel blockers, diuretics, alpha blockers or other vasodilator, angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and antidiabetic agents. Additionally, use of non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRI), and non-study protonpump inhibitors (PPI) was collected at baseline, but no information on other drugs was available. Therefore, we

analysed results by the number of cardiovascular drug categories for the primary analysis and we report total number of drug categories as supplemental information. No information on specific molecule or dosing was collected. Based on the distribution of number of cardiovascular drugs, patients were categorized in four groups of roughly equal size for further analysis.

Concomitant medical conditions

We collected information on the presence of concomitant medical conditions in the following nine categories: cancer, gastro-intestinal disease, conditions associated with cardiometabolic risk, respiratory disease, renal and genitourinary disease, liver disease, neurocognitive disease, cardiovascular disease other than CAD or PAD, and musculoskeletal disease. We combined data from the screening and randomization assessment, the functional questionnaires, and relevant follow-up events that were associated with underlying chronic conditions. Definitions of concomitant medical conditions are shown in **supplementary table S4**. To avoid double-counting, we counted the number of affected organ systems rather than the individual number of conditions. Thus, for each category, patients were counted once if they had at least one diagnosis in this category.

Outcomes

We used prespecified outcome definitions as detailed in the COMPASS protocol. The primary efficacy outcome was the composite of myocardial infarction, stroke, or cardiovascular death. The primary safety outcome was major bleeding defined as the composite of fatal bleeding, symptomatic bleeding into a critical organ, surgical site bleeding requiring reoperation, or requiring hospitalization (including presentation to an acute care facility

without an overnight stay). A prespecified net clinical benefit outcome was the composite of cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ[10].

Statistical analysis

We present baseline demographics in four categories of number of cardiovascular medications and of concomitant medical conditions. Study outcomes were analysed based on time to first event for the intention-to-treat population. Annualized event rates were calculated as number of patients with an outcome per total number of patient-years of follow-up.

Univariate Cox proportional hazards regression models were used to compare study outcomes according to number of cardiovascular medications, any medications, and number of concomitant conditions. Stratified Cox proportional hazards models were used to estimate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the comparison of rivaroxaban plus aspirin vs aspirin alone in subgroups of number of cardiovascular drugs and comorbidities with log-rank tests to evaluate significance. 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 use of cardiovascular medications 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 either cardiovascular medications or comorbidities, and

treatment with rivaroxaban and aspirin vs aspirin alone. As a sensitivity analysis, we additionally calculated shrinkage estimators for the analysis. When comparing multiple subgroups in a post-hoc analysis, shrinkage analysis takes into account the overall population data to reduce the effect of random sampling effects within subgroups. Therefore, shrinkage analysis provides better estimates of the true treatment effect. Shrinkage estimates of the treatment effect were obtained via bayesian hierarchical modeling analysis, considering the estimates from the subgroups that made up the overall COMPASS population. The shrinkage analysis was performed using the "bayes-meta" package in R version 3.5.1 (R Foundation for Statistical Computing), and all other analyses were conducted using SAS version 9.4 (SAS Institute). All reported p values are two-sided. There was no correction for multiple comparisons.

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

Number of drugs and comorbidities: polypharmacy and multimorbidity are frequent in patients with atherosclerotic disease

Baseline information on concomitant cardiovascular drug use was available for all of the 27,395 individuals randomized in COMPASS, and information for any medication including

prespecified non-cardiovascular drugs was available in 27,388 patients (99.97%). Mean follow-up was 23 months.

Figure 1 shows the distribution of number of cardiovascular medications (1A) and of number of concomitant medical conditions (1B). On top of aspirin treatment and study drug, which included rivaroxaban or placebo as well as – in a subset of patients – study PPI or placebo, 74.8% of patients took at least three additional cardiovascular drug classes, and 16.9% took five or more cardiovascular drugs. When also including prespecified non-cardiovascular medications, 82% of patients took at least 3 additional medications, and 11% of patients received six or more drug categories per day. Concomitant medical conditions were frequent: 59.4% of participants had three or more concomitant medical conditions, and 11.6% had five or more comorbidities.

Table 1 shows baseline characteristics by number of cardiovascular medications. As expected, patients with higher numbers of cardiovascular medications were more likely to have other cardiovascular diseases of risk factors, such as heart failure, renal insufficiency, peripheral artery disease, hypertension, and diabetes. However, higher number of drugs was not associated with age (p=0.15). Similarly, occurrence of cardiovascular risk factors was higher in patients with more comorbid conditions (**supplemental Table S1**). Patients with more non-cardiac comorbidities were more likely to also have heart failure or peripheral arterial disease, while coronary artery disease was less frequent. Use of cardiovascular medications was higher in patients with more comorbidities, except for lipid-lowering agents.

Risk of stroke, myocardial, or cardiovascular death and risk of major bleeding by number of drugs and comorbidities

Mean follow-up was 23 months. The risk of the primary endpoint increased with higher number of cardiovascular drugs (**Figure 2A**). Compared with those with 0-2 cardiovascular drugs, patients taking five or more had a 74% higher incidence rate of the combination of stroke, myocardial infarction, or cardiovascular death (HR 1.74, 95%CI 1.47-2.05, p<0.0001). A similar increase in cardiovascular events, was found when also considering prespecified non-cardiovascular medications (data not shown).

In contrast, the risk of major bleeding in the overall population did not increase with the number of cardiovascular medications (HR 1.17, 95%CI 0.93-1.46 for 0-2 *vs* 5 or more cardiovascular medications). When including prespecified non-cardiovascular medications, there was an increase in bleeding risk only in those patients taking five or more drugs as compared to 0-2 drugs (HR 1.31, 95%CI 1.05-1.63).

A higher number of comorbidities was associated with an increased risk for both the primary efficacy outcome and for major bleeding. Compared to patients with 0-1 comorbidities, patients with 4 or more comorbidities had more than a twofold higher risk of stroke, myocardial infarction, or cardiovascular death (HR 2.45, 95%CI 2.01-2.99, p<0.0001) and of major bleeding (HR 2.34, 95%CI 1.79-2.06, p<0.0001) (**Figure 2B**). Kaplan-Meier curves of the primary efficacy and safety outcome in relation to the number of concomitant drugs and comorbidities are shown in **Figure 3**.

Efficacy of the combination of rivaroxaban and aspirin compared with aspirin alone by number of drugs and comorbidities

Rates of the primary efficacy endpoint increased with higher number of concomitant cardiovascular medications and with more comorbidities in aspirin-treated patients as well as in rivaroxaban-treated patients. However, the efficacy of adding rivaroxaban to aspirin was not affected by the number of cardiovascular drugs (p for interaction 0.58) or the number of comorbidities (p for interaction 0.58) (**Figure 4**).

Regardless of the number of drugs, event rates were lower in patients receiving rivaroxaban plus aspirin compared with aspirin alone with a 20 to 30% relative risk reduction, consistent with the overall COMPASS results (**Figure 4A**). Because of the higher absolute event rate, the absolute reduction was highest in patients with the highest number of cardiovascular drugs (1.3%/yr ARR in patients with ≥5 vs 0.4%/yr ARR in patients with 0-2 drugs) (**Table 2, Figure 5A**). This translates into a number needed to treat (NNT) of 77 in patients five or more vs 250 in patients taking 0-2 cardiovascular drugs. The number of comorbidities did not affect the absolute risk reduction (0.7%/yr ARR in patients with 0-1 as well as in patients with 4-8 comorbidities, NNT 142). Additionally, shrinkage estimates confirmed that the effect of adding low-dose rivaroxaban to aspirin were consistent within each subgroup of number of cardiovascular medications (**Table 2**).

Safety and net clinical benefit of the combination of rivaroxaban and aspirin compared with aspirin alone by number of drugs and comorbidities

Rates of major bleeding were higher in patients who received rivaroxaban on top of aspirin, without an interaction between number of cardiovascular drugs and bleeding risk (p for

interaction 0.55) and the number of comorbidities and bleeding risk (p for interaction 0.64) (**Figures 3B and 4B**)

The relative reduction in the prespecified net clinical outcome was also independent of the number of drugs and the number of comorbidities (p for interaction 0.80 and 0.48, respectively). There was a larger absolute reduction in the net clinical outcome in patients with the highest number of drugs (1.1% ARR in patients with ≥5 vs 0.4% ARR in patients with 0-2 cardiovascular drugs, NNT of 91 vs 250) (**Table 2, Figure 5B**).

Effect of types of cardiovascular medication on the efficacy and safety rivaroxaban

In a non-adjusted analysis, there was no interaction between any individual category of cardiovascular medication and the relative efficacy of rivaroxaban plus aspirin vs aspirin alone. However, use of NSAIDs was associated with a more pronounced increase in major bleeding (HR of 3.9, 95%CI 1.7-8.8 in patients with NSAIDs, vs 1.6, 95%CI 1.3-2.0 in patients without NSAIDs) with a p value for interaction bordering on significance (p interaction = 0.05). Conversely, use of diuretics was associated with a lower increase in bleeding risk. There was no suggestion of higher crude bleeding rates in patients treated with selective serotonin reuptake inhibitors (SSRI), and no interaction between SSRI use and the relative safety of rivaroxaban on top of aspirin (**Supplemental Table S2**)

Effect of types of comorbidities on the efficacy and safety of rivaroxaban

As shown in **Supplemental Table S3**, there was no interaction between individual types of comorbidities and the relative efficacy of safety of rivaroxaban plus aspirin vs aspirin alone, with the exception of a statistically significant interaction in cancer patients where there was

a higher rate of the primary efficacy outcome in patients treated with rivaroxaban on top of aspirin.

Discussion

Adding twice daily low-dose rivaroxaban on top of aspirin reduces ischemic events and all-cause mortality in patients with coronary and/or peripheral artery disease[6]. Because this reduction in mortality and non-fatal thromboembolic events comes at the cost of a higher pill burden (two additional pills per day) and an increase in the risk of major, but not fatal, bleeding, physicians should take into account the patients' individual risk of ischemic and bleeding events when considering whether to add low-dose rivaroxaban[1]. The number and type of concomitant drugs and the number of concomitant medical conditions are often considered as additional risk factors for ischemic as well as bleeding events.

Our study confirms that in patients with stable atherosclerotic disease, polypharmacy (defined as at least five pills) and multimorbidity are very frequent. This corroborates previous studies in patients with atherosclerotic disease or other cardiovascular conditions[4].

In this analysis, we demonstrate that the efficacy and the safety of low-dose rivaroxaban added to aspirin is consistent regardless of the types or the number of cardiovascular drugs that patients are already taking and of the number of comorbidities. Notably, the risk for cardiovascular events (myocardial infarction, stroke, or cardiovascular death) increased with increasing number of concomitant drugs at baseline as well as with more comorbidities. In contrast, bleeding risk, which is often a concern in frailer patients, did not increase with

higher number of concomitant cardiovascular drugs but was higher in multimorbid patients. Thus, our analysis shows the highest absolute reduction in net clinical outcomes in the patient group with the highest number of concomitant baseline drugs.

In an exploratory, non-adjusted analysis, individual classes of cardiovascular drugs did not affect the relative efficacy or safety of rivaroxaban, with the potential exception of NSAIDs, for which the p value for interaction was borderline significant (p=0.05). Although this finding should be interpreted with caution because it represents a subgroup analysis, prior studies have also found that the use of NSAID was associated higher rates of major bleeding[11]. Therefore, when considering intensified antithrombotic therapies, physicians should be aware of the bleeding risk associated with chronic NSAID use. A separate, previously published analysis of the randomization between placebo and proton pump inhibitor (PPI) in the COMPASS study found no interaction between NSAID use and bleeding in patients randomized to PPI compared to placebo. In contrast, we did not observe an increased bleeding risk in patients treated with selective serotonin reuptake inhibitors, as had been reported in other studies.

While our findings are informative for patients and physicians, our study has several limitations. Our analysis was a not pre-defined post-hoc secondary analysis of a randomized trial. Details on concomitant drug use in the COMPASS trial were limited as only cardiovascular drugs, PPI, and NSAIDS were systematically collected. We only had baseline information on drug prescriptions and were not able to correct for changes in the treatment during the trial. However, most cardiovascular drugs as well as the prespecified non-cardiovascular drugs are chronic therapies that often persist over years. Importantly, no

information is available on true adherence, dose, and frequency of concomitant medications. However, this is reflective of real-world practice where discrepancies between prescribed therapy and effectively used therapy may exist.

In the COMPASS study, there was detailed information on cardiovascular medication at baseline, but only a few categories of non-cardiovascular medication were captured. Thus, our data are likely to underestimate the actual number of drugs used in patients and the occurrence of polypharmacy.

It is uncertain to which extent more detailed information on non-cardiovascular drugs would affect our findings. In order to gather information on non-cardiovascular conditions that may require chronic pharmacotherapy, we also reported outcomes by the number of comorbidities. Both the number of medications and the number of concomitant medical conditions are often considered to be markers of frailty, and concepts of polypharmacy and multimorbidity are closely linked; patients with more non-cardiovascular diseases are more likely to require more types of medical treatment. Therefore, number of (cardiovascular) medications and the number of comorbidities give complementary information about the severity of the patients underlying risk factor status, extent of the cardiovascular disease, and non-cardiovascular conditions. This is illustrated by a comparable increase in the risk of cardiovascular death and cardiovascular events with increasing number of medications as well as comorbidities.

Severe comorbidities (severe renal insufficiency, severe liver disease and diseases with expected poor short-term prognosis) were excluded, as well as any condition expected to lead to an unacceptable bleeding risk. Therefore, our findings may not apply to patients with very severe comorbidities.

There are two implications of our finding. First, our analysis confirms that a large proportion of stable vascular patients take a high number of (cardiovascular) drugs and suffer from multiple comorbidities. Because compliance and persistence with prescribed drugs is different in clinical trials as compared to clinical practice[12], measures to ensure patient's adherence to the therapy will be needed. One option to reduce pill burden is combination therapies (poly-pill), which are currently also being evaluated in clinical trials[13-15].

Secondly, the relative efficacy, safety, and net clinical benefit of adding low-dose rivaroxaban to aspirin in patients with stable vascular diseases were not affected by the number of cardiovascular drugs nor by the number of comorbidities. Hence, a high number of pills or a complex medical history should by itself not discourage physicians and patients to add extra therapies, as patients with greater number of cardiovascular drugs had the largest absolute benefit from intensified antithrombotic therapy.

Conclusion

In conclusion, patients receiving multiple drugs and with multimorbidity have a higher risk of cardiovascular events. However, the efficacy, safety, and net clinical benefit of adding low-dose rivaroxaban to aspirin in patients with stable vascular diseases were not affected by the number of drugs or comorbidities. The presence of multiple comorbidities or the need for several drugs should not dissuade the addition of low-dose rivaroxaban to aspirin in otherwise eligible patients.

Conflict of Interest statement

The COMPASS study was sponsored by Bayer.

TV reports honoraria for lectures, presentations, support for meeting attendance and/or participation in advisory boards from Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Sanofi Aventis, Leo Pharma.

PV reports institutional research grants from Bayer and Nordic Pharma; honoraria for advisory boards and/or consultancy from Boehringer Ingelheim, Bayer, BMS, Pfizer, Daiichi Sankyo, Anthos Therapeutics; honoraria for lectures from Boehringer Ingelheim, Bayer, BMS, Pfizer, Daiichi Sankyo; and participation in DSMB or advisory board for Boehringer Ingelheim and Bayer.

SSA reports consulting and speaking fees from Bayer and Janssen and support for attending meetings from Bayer.

DPL reports support for travel to attend meeting from Bayer.

KAAF reports grants or contracts from Bayer, Janssen; consulting fees and honoraria for lectures from Bayer.

DLB reports personal fees from Bayer, during the conduct of the study; grants from Amarin, grants from AstraZeneca, grants from Bristol-Myers Squibb, grants from Eisai, grants from Ethicon, grants from Medtronic, grants from sanofi aventis, grants from The Medicines Company, other from FlowCo, grants and other from PLx Pharma, other from Takeda, personal fees from Duke Clinical Research Institute, personal fees from Mayo Clinic, personal fees from Population Health Research Institute, personal fees, non-financial support and other from American College of Cardiology, personal fees from Belvoir Publications, personal fees from Slack Publications, personal fees from WebMD, personal fees from Elsevier, other from Medscape Cardiology, other from Regado Biosciences, other from Boston VA Research Institute, personal fees and non-financial support from Society of Cardiovascular Patient Care, non-financial support from American Heart Association, personal fees from HMP Global, grants from Roche, personal fees from Harvard Clinical Research Institute (now Baim Institute for Clinical Research), other from Clinical Cardiology, personal fees from Journal of the American College of Cardiology, other from VA, grants from Pfizer, grants from Forest Laboratories/AstraZeneca, grants from Ischemix, other from St. Jude Medical (now Abbott), other from Biotronik, grants and other from Cardax, other from Boston Scientific, grants from Amgen, grants from Lilly, grants from Chiesi, grants from Ironwood, personal fees from Cleveland Clinic, personal fees from Mount Sinai School of Medicine, other from Merck, grants from Abbott, grants from Regeneron, other from Svelte, grants and other from PhaseBio, grants from

Idorsia, grants from Synaptic, personal fees from TobeSoft, grants, personal fees and other from Boehringer Ingelheim, personal fees from Bayer, grants and other from Novo Nordisk, grants from Fractyl, personal fees from Medtelligence/ReachMD, personal fees from CSL Behring, grants and other from Cereno Scientific, grants from Afimmune, grants from Ferring Pharmaceuticals, other from CSI, grants from Lexicon, personal fees from MJH Life Sciences, personal fees from Level Ex, grants from Contego Medical, grants and other from CellProthera, personal fees from K2P, personal fees from Canadian Medical and Surgical Knowledge Translation Research Group, grants and other from MyoKardia/BMS, grants from Owkin, grants from HLS Therapeutics, grants and other from Janssen, grants from 89Bio, grants and other from Novo Nordisk, grants from Garmin, grants and other from Novartis, outside the submitted work; .Dr. Bhatt reports grants from Amarin, grants from AstraZeneca, grants from Bristol-Myers Squibb, grants from Eisai, grants from Ethicon, grants from Medtronic, grants from sanofi aventis, grants from The Medicines Company, other from FlowCo, other from PLx Pharma, other from Takeda, personal fees from Duke Clinical Research Institute, personal fees from Mayo Clinic, personal fees from Population Health Research Institute, personal fees, non-financial support and other from American College of Cardiology, personal fees from Belvoir Publications, personal fees from Slack Publications, personal fees from WebMD, personal fees from Elsevier, other from Medscape Cardiology, other from Regado Biosciences, other from Boston VA Research Institute, personal fees and non-financial support from Society of Cardiovascular Patient Care, non-financial support from American Heart Association, personal fees from HMP Global, grants from Roche, personal fees from Harvard Clinical Research Institute (now Baim Institute for Clinical Research), other from Clinical Cardiology, personal fees from Journal of the American College of Cardiology, other from VA, grants from Pfizer, grants from Forest Laboratories/AstraZeneca, grants from Ischemix, other from St. Jude Medical (now Abbott), other from Biotronik, other from Cardax, other from Boston Scientific, grants from Amgen, grants from Lilly, grants from Chiesi, grants from Ironwood, personal fees from Cleveland Clinic, personal fees from Mount Sinai School of Medicine, other from Merck, grants from Abbott, grants from Regeneron, other from Svelte, grants and other from PhaseBio, grants from Idorsia, grants from Synaptic, personal fees from TobeSoft, personal fees and other from Boehringer Ingelheim, personal fees from Bayer, other from Novo Nordisk, grants from Fractyl, personal fees from Medtelligence/ReachMD, personal fees from CSL Behring, other from Cereno Scientific, grants from Afimmune, personal fees from Ferring Pharmaceuticals, other from CSI, outside the submitted work;

AA reports consulting fees from Bayer, Daiichi Sankyo.

MA reports participation in advisory board or data safety monitoring board for Boehringer Ingelheim, BMS, Bayer, Daiichi Sankyo, Roche diagnostics, Milestone Pharmaceuticals.

VA reports consulting fees from Bayer, AstraZeneca, Boehringer Ingelheim, honoraria as a speaker and for expert testimony and support for attending meetings from Bayer.

PW reports consulting fees and honoraria for speaker bureaus from Bayer.

EM and SDB are Bayer employees and EM reports Bayer employee stock options.

SY reports grants to his institution for the COMPASS trial, and honoraria, consulting fees, and support for attending meetings from Bayer for lectures on the COMPASS trial.

SJC reports grants from Bayer AG during the conduct of the study; personal fees from BMS, personal fees from Pfizer, personal fees from Portola, personal fees from Boehringer Ingelheim, personal fees from Servier, personal fees from Daiichi Sankyo, and personal fees from Medtronic outside the submitted work.

JWE reports grants to the institution from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myer-Squibb, Glaxo-Smith-Kline, Pfizer, Janssen, Sanofi-Aventis; and honoraria for lectures from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myer-Squibb, Daiichi-Sankyo, Eli-Lilly, Glaxo-Smith-Kline, Pfizer, Janssen, Sanofi-Aventis, Servier.

JB reports participation in Bayer steering committee (adjudication) for the XATOA and XATOC studies.

References

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, Group ESCSD. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;**41**(3):407-477.
2. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Rother J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I, Group ESCSD. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;**39**(9):763-816.
3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O, Group ESCSD. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;**41**(1):111-188.
4. Forman DE, Maurer MS, Boyd C, Brindis R, Salive ME, Horne FM, Bell SP, Fulmer T, Reuben DB, Zieman S, Rich MW. Multimorbidity in Older Adults With Cardiovascular Disease. J Am Coll Cardiol 2018;**71**(19):2149-2161.
5. Vetrano DL, Palmer K, Marengoni A, Marzetti E, Lattanzio F, Roller-Wirnsberger R, Lopez Samaniego L, Rodriguez-Manas L, Bernabei R, Onder G, Joint Action AWPG. Frailty and Multimorbidity: A Systematic Review and Meta-analysis. J Gerontol A Biol Sci Med Sci 2019;**74**(5):659-666.
6. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S, Investigators C. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;**377**(14):1319-1330.
7. Chen N, Alam AB, Lutsey PL, MacLehose RF, Claxton JS, Chen LY, Chamberlain AM, Alonso A. Polypharmacy, Adverse Outcomes, and Treatment Effectiveness in Patients >/=75 With Atrial Fibrillation. J Am Heart Assoc 2020;**9**(11):e015089.
8. Abolbashari M, Macaulay TE, Whayne TF, Mukherjee D, Saha S. Polypharmacy in Cardiovascular Medicine: Problems and Promises! Cardiovasc Hematol Agents Med Chem 2017;**15**(1):31-39.
9. Viscogliosi G, Donfrancesco C, Lo Noce C, Vanuzzo D, Carle F, Giampaoli S, Palmieri L. Prevalence and Correlates of Statin Underuse for Secondary Prevention of Cardiovascular

Disease in Older Adults 65-79 Years of Age: The Italian Health Examination Survey 2008-2012. Rejuvenation Res 2020;**23**(5):394-400.
10. Bosch J, Eikelboom JW, Connolly SJ, Bruns NC, Lanius V, Yuan F, Misselwitz F, Chen E, Diaz R, Alings M, Lonn EM, Widimsky P, Hori M, Avezum A, Piegas LS, Bhatt DL, Branch KRH, Probstfield JL, Liang Y, Liu L, Zhu J, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Fox KAA, Kakkar A, Parkhomenko AN, Ertl G, Stork S, Keltai K, Keltai M, Ryden L, Dagenais GR, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Ha JW, Tonkin AM, Varigos JD, Lewis BS, Felix C, Yusoff K, Steg PG, Aboyans V, Metsarinne KP, Anand SS, Hart RG, Lamy A, Moayyedi P, Leong DP, Sharma M, Yusuf S. Rationale, Design and Baseline Characteristics of Participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial. Can J Cardiol 2017;**33**(8):1027-1035.
11. Schjerning Olsen AM, Gislason GH, McGettigan P, Fosbol E, Sorensen R, Hansen ML, Kober L, Torp-Pedersen C, Lamberts M. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA 2015;**313**(8):805-14.
12. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Reiner Z, Keil U, Group ES. EUROASPIRE III. Management of cardiovascular risk factors in asymptomatic high-risk patients in general practice: cross-sectional survey in 12 European countries. Eur J Cardiovasc Prev Rehabil 2010;**17**(5):530-40.
13. Munoz D, Uzoije P, Reynolds C, Miller R, Walkley D, Pappalardo S, Tousey P, Munro H, Gonzales H, Song W, White C, Blot WJ, Wang TJ. Polypill for Cardiovascular Disease Prevention in an Underserved Population. N Engl J Med 2019;**381**(12):1114-1123.
14. Yusuf S, Joseph P, Dans A, Gao P, Teo K, Xavier D, Lopez-Jaramillo P, Yusoff K, Santoso A, Gamra H, Talukder S, Christou C, Girish P, Yeates K, Xavier F, Dagenais G, Rocha C, McCready T, Tyrwhitt J, Bosch J, Pais P, International Polycap Study I. Polypill with or without Aspirin in Persons without Cardiovascular Disease. N Engl J Med 2020.
15. Roshandel G, Khoshnia M, Poustchi H, Hemming K, Kamangar F, Gharavi A, Ostovaneh MR, Nateghi A, Majed M, Navabakhsh B, Merat S, Pourshams A, Nalini M, Malekzadeh F, Sadeghi M, Mohammadifard N, Sarrafzadegan N, Naemi-Tabiei M, Fazel A, Brennan P, Etemadi A, Boffetta P, Thomas N, Marshall T, Cheng KK, Malekzadeh R. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. Lancet 2019;**394**(10199):672-683.

Table 1. Baseline characteristics by number of cardiovascular medications

	Number of cardiovascular medications				
	0-2 (N=6883)	3 (N=8774)	4 (N=7116)	5-7 (N=4622)	P value
Age (yr)	68.3±8.1	68.2±7.8	68.2±7.9	68.1±7.9	0.15
Female sex	1493 (21.7)	1774 (20.2)	1616 (22.7)	1137 (24.6)	<0.0001
Body-mass index (kg/m^2)	27.0±4.3	28.0±4.4	28.8±4.7	30.2±5.2	<0.0001
Systolic blood pressure (mm Hg)	135±17	135±17	136±18	138±18	<0.0001
Diastolic blood pressure (mm Hg)	78±10	78±10	77±10	77±10	<0.0001
Total cholesterol (mg/dl)	78.2±9.9	77.8±9.8	77.5±10.1	77.3±10.3	<0.0001
Current smoker	1652 (24.0)	1895 (21.6)	1471 (20.7)	849 (18.4)	<0.0001
Hypertension	3895 (56.6)	6565 (74.8)	5953 (83.7)	4219 (91.3)	<0.0001
Diabetes	1278 (18.6)	2187 (24.9)	3389 (47.6)	3487 (75.4)	<0.0001
Physical activity (min/wk)	1587±2567	1561±2422	1445±2159	1389±2195	<0.0001
Previous stroke	209 (3.0)	286 (3.3)	286 (4.0)	251 (5.4)	<0.0001
Previous myocardial infarction	3639 (52.9)	5749 (65.5)	4730 (66.5)	2910 (63.0)	<0.0001
Heart failure	907 (13.2)	1769 (20.2)	1777 (25.0)	1449 (31.4)	<0.0001
Coronary artery disease	5632 (81.8)	8184 (93.3)	6662 (93.6)	4346 (94.0)	<0.0001
Peripheral arterial disease	2185 (31.7)	2026 (23.1)	1824 (25.6)	1435 (31.0)	<0.0001
Estimated GFR					
<30 ml/min	38 (0.6)	54 (0.6)	56 (0.8)	95 (2.1)	<0.0001
30 to <60 ml/min	1226 (17.8)	1752 (20.0)	1721 (24.2)	1334 (28.9)	<0.0001
≥60 ml/min	5618 (81.6)	6966 (79.4)	5335 (75.0)	3192 (69.1)	<0.0001
Race					
White	3843 (55.8)	5560 (63.4)	4586 (64.4)	3038 (65.7)	<0.0001
Black	46 (0.7)	69 (0.8)	71 (1.0)	76 (1.6)	<0.0001
Asian	1400 (20.3)	1288 (14.7)	995 (14.0)	586 (12.7)	<0.0001
Other	1594 (23.2)	1857 (21.2)	1464 (20.6)	922 (19.9)	<0.0001
Geographic region					
North America	946 (13.7)	1262 (14.4)	1028 (14.4)	682 (14.8)	0.44
South America	1663 (24.2)	1966 (22.4)	1582 (22.2)	933 (20.2)	<0.0001
Western Europe, Israel, Australia, or South Africa	2284 (33.2)	2906 (33.1)	2119 (29.8)	1246 (27.0)	<0.0001
Eastern Europe	654 (9.5)	1442 (16.4)	1491 (21.0)	1236 (26.7)	<0.0001

	Number of cardiovascular medications				
	0-2 (N=6883)	3 (N=8774)	4 (N=7116)	5-7 (N=4622)	P value
Asia-Pacific	1336 (19.4)	1198 (13.7)	896 (12.6)	525 (11.4)	<0.0001
Cardiovascular medications					
Lipid-lowering agent	4976 (72.3)	8211 (93.6)	6860 (96.4)	4554 (98.5)	<0.0001
Beta blocker	2439 (35.4)	6475 (73.8)	6001 (84.3)	4269 (92.4)	<0.0001
Calcium-channel blocker	592 (8.6)	1390 (15.8)	2359 (33.2)	2928 (63.3)	<0.0001
Diuretic	304 (4.4)	1326 (15.1)	3038 (42.7)	3471 (75.1)	<0.0001
Alpha blocker or other vasodilator	219 (3.2)	644 (7.3)	1040 (14.6)	1534 (33.2)	<0.0001
ACE inhibitor or ARB	2249 (32.7)	6705 (76.4)	6196 (87.1)	4368 (94.5)	<0.0001
Hypoglycemic agent	702 (10.2)	1571 (17.9)	2970 (41.7)	3312 (71.7)	<0.0001
Other medications					
NSAID	392 (5.7)	433 (4.9)	358 (5.0)	287 (6.2)	0.005
SSRI	233 (3.4)	295 (3.4)	268 (3.8)	233 (5.0)	<0.0001
Non-study PPI	2224 (32.3)	3085 (35.2)	2674 (37.6)	1815 (39.3)	<0.0001

For continuous variables, plus-minus values are mean ± standard deviation. For categorical variables, frequency (percent) are shown. P value is from the Wilcoxon 2-sample test for continuous variables, and Pearson chi-square test for categorical variables. GFR: glomerular filtration rate. ACE: angiotensin converting enzyme. ARB: angiotensin-receptor blocker. NSAID: non-steroidal anti-inflammatory drugs. SSRI: selective serotonin reuptake inhibitor. PPI: proton pump inhibitor.

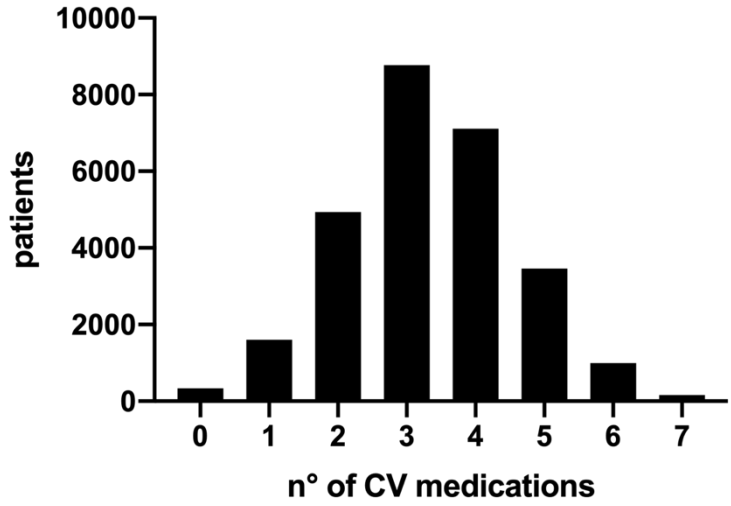
Table 2. Effect of antithrombotic therapies by number of cardiovascular medications and number of comorbidities

	Rivaroxaban plus Aspirin (N=9152)		Aspirin Alone (N=9126)		Rivaroxaban plus Aspirin vs. Aspirin Alone			Shrinkage Estimates
	No. of first events / patients (%)	Annual rate, %/yr	No. of first events / patients (%)	Annual rate, %/yr	Hazard Ratio (95% CI)	P value	P value for interaction	Hazard Ratio (95% CI)
Primary efficacy outcome: **CV death, stroke, or myocardial infarction**								
Number of cardiovascular medications							0.58	
0-2	73 / 2327 (3.1)	1.7	90 / 2256 (4.0)	2.1	0.80 (0.58-1.08)	0.15		0.77 (0.60-0.96)
3	109 / 2943 (3.7)	1.9	153 / 2935 (5.2)	2.7	0.71 (0.56-0.91)	0.006		0.73 (0.60-0.88)
4	118 / 2384 (4.9)	2.6	135 / 2357 (5.7)	3.0	0.85 (0.66-1.09)	0.19		0.80 (0.64-0.97)
5-7	79 / 1498 (5.3)	2.7	118 / 1578 (7.5)	4.0	0.67 (0.50-0.89)	0.005		0.72 (0.56-0.88)
Number of comorbidities							0.58	
0-1	30 / 1377 (2.2)	1.2	50 / 1414 (3.5)	1.9	0.61 (0.39-0.96)	0.03		0.71 (0.48-0.91)
2	61 / 2264 (2.7)	1.4	90 / 2318 (3.9)	2.1	0.70 (0.51-0.97)	0.03		0.73 (0.56-0.92)
3	108 / 2652 (4.1)	2.2	145 / 2577 (5.6)	3.0	0.72 (0.56-0.92)	0.01		0.73 (0.58-0.88)
4-8	180 / 2859 (6.3)	3.2	211 / 2817 (7.5)	3.9	0.83 (0.68-1.01)	0.06		0.79 (0.65-0.94)
Primary safety outcome: **Major bleeding**								
Number of cardiovascular medications							0.55	
0-2	71 / 2327 (3.1)	1.7	40 / 2256 (1.8)	0.9	1.77 (1.20-2.61)	0.003		1.73 (1.26-2.26)
3	89 / 2943 (3.0)	1.6	47 / 2935 (1.6)	0.8	1.92 (1.35-2.73)	0.0002		1.80 (1.31-2.33)
4	79 / 2384 (3.3)	1.7	44 / 2357 (1.9)	1.0	1.76 (1.22-2.55)	0.002		1.74 (1.27-2.26)
5-7	49 / 1498 (3.3)	1.7	39 / 1578 (2.5)	1.3	1.30 (0.85-1.97)	0.23		1.55 (1.01-2.05)
Number of comorbidities							0.64	
0-1	30 / 1377 (2.2)	1.2	13 / 1414 (0.9)	0.5	2.47 (1.28-4.73)	0.005		1.94 (1.18-2.94)
2	54 / 2264 (2.4)	1.3	36 / 2318 (1.6)	0.8	1.54 (1.01-2.35)	0.04		1.67 (1.15-2.20)
3	82 / 2652 (3.1)	1.7	44 / 2577 (1.7)	0.9	1.81 (1.25-2.61)	0.001		1.77 (1.28-2.29)

	Rivaroxaban plus Aspirin (N=9152)		Aspirin Alone (N=9126)		Rivaroxaban plus Aspirin vs. Aspirin Alone			Shrinkage Estimates
	No. of first events / patients (%)	Annual rate, %/yr	No. of first events / patients (%)	Annual rate, %/yr	Hazard Ratio (95% CI)	P value	P value for interaction	Hazard Ratio (95% CI)
4-8	122 / 2859 (4.3)	2.2	77 / 2817 (2.7)	1.4	1.57 (1.18-2.08)	0.002		1.65 (1.24-2.05)
Net clinical benefit outcome: **CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ**								
Number of cardiovascular medications							0.80	
0-2	87 / 2327 (3.7)	2.0	100 / 2256 (4.4)	2.4	0.85 (0.64-1.14)	0.28		0.82 (0.66-1.00)
3	124 / 2943 (4.2)	2.2	161 / 2935 (5.5)	2.9	0.77 (0.61-0.97)	0.03		0.79 (0.65-0.93)
4	130 / 2384 (5.5)	2.9	149 / 2357 (6.3)	3.3	0.85 (0.67-1.07)	0.17		0.82 (0.68-0.99)
5-7	90 / 1498 (6.0)	3.1	124 / 1578 (7.9)	4.2	0.73 (0.55-0.95)	0.02		0.78 (0.62-0.94)
Number of comorbidities							0.48	
0-1	37 / 1377 (2.7)	1.4	53 / 1414 (3.7)	2.0	0.71 (0.46-1.08)	0.10		0.76 (0.54-0.97)
2	69 / 2264 (3.0)	1.6	105 / 2318 (4.5)	2.4	0.68 (0.50-0.92)	0.01		0.74 (0.56-0.92)
3	120 / 2652 (4.5)	2.4	150 / 2577 (5.8)	3.1	0.77 (0.61-0.98)	0.03		0.78 (0.63-0.93)
4-8	205 / 2859 (7.2)	3.7	226 / 2817 (8.0)	4.2	0.88 (0.73-1.06)	0.19		0.84 (0.71-1.00)

CV: cardiovascular

Figure 1. Distribution of number of cardiovascular (CV) medications (A) and number of concomitant medical conditions (B). Total number of patients is 27,395



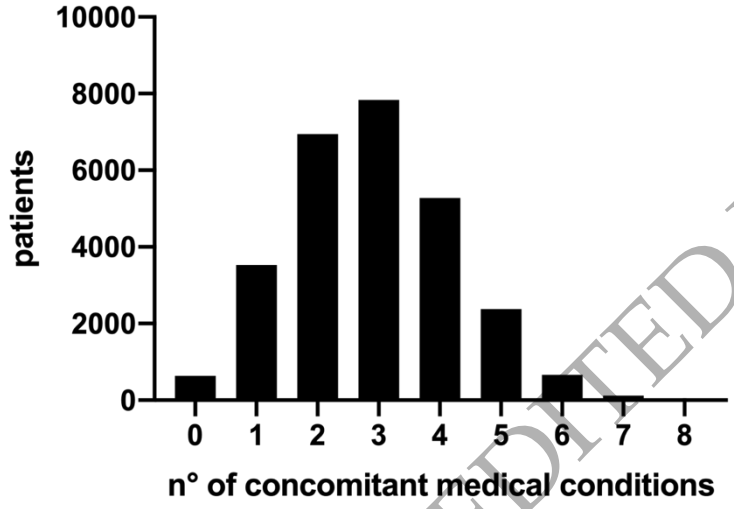
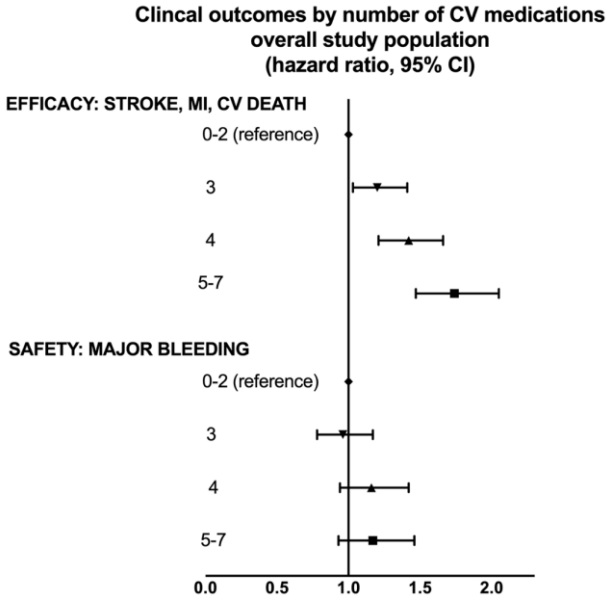
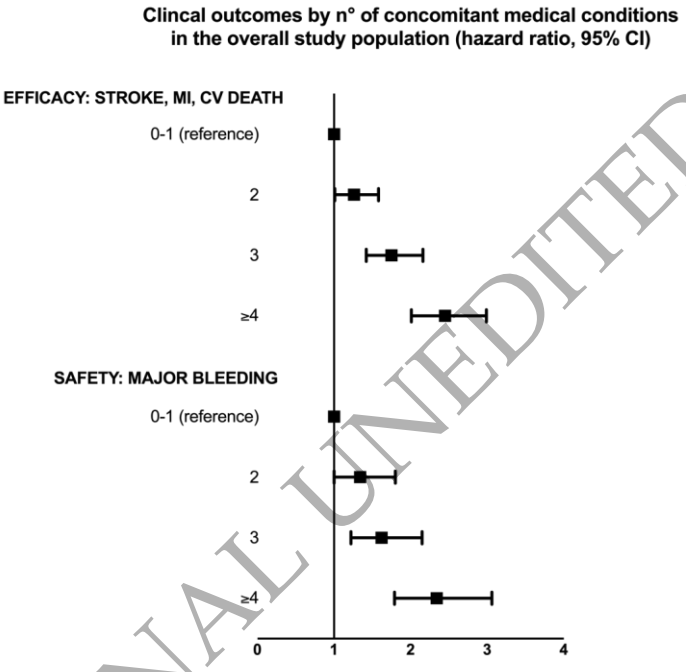


Figure 2. Outcomes by number of cardiovascular (CV) medications (A) and by number of concomitant medical conditions (B) in the overall study population



A



B

Figure 3. Kaplan-Meier curves of primary efficacy outcome (A) and major bleeding (B) by number of cardiovascular (CV) medications, any medications, and number of concomitant medical conditions in the overall study population

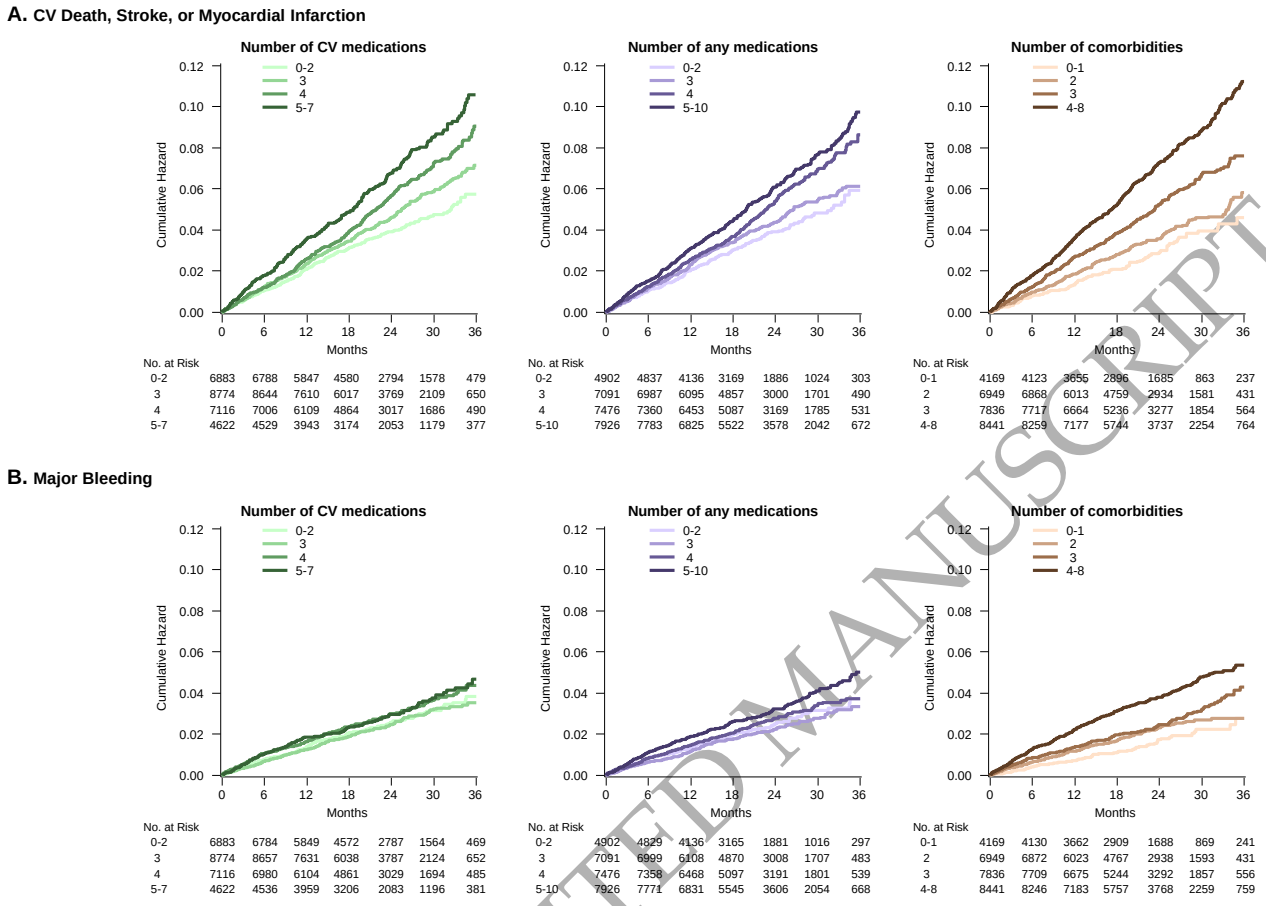
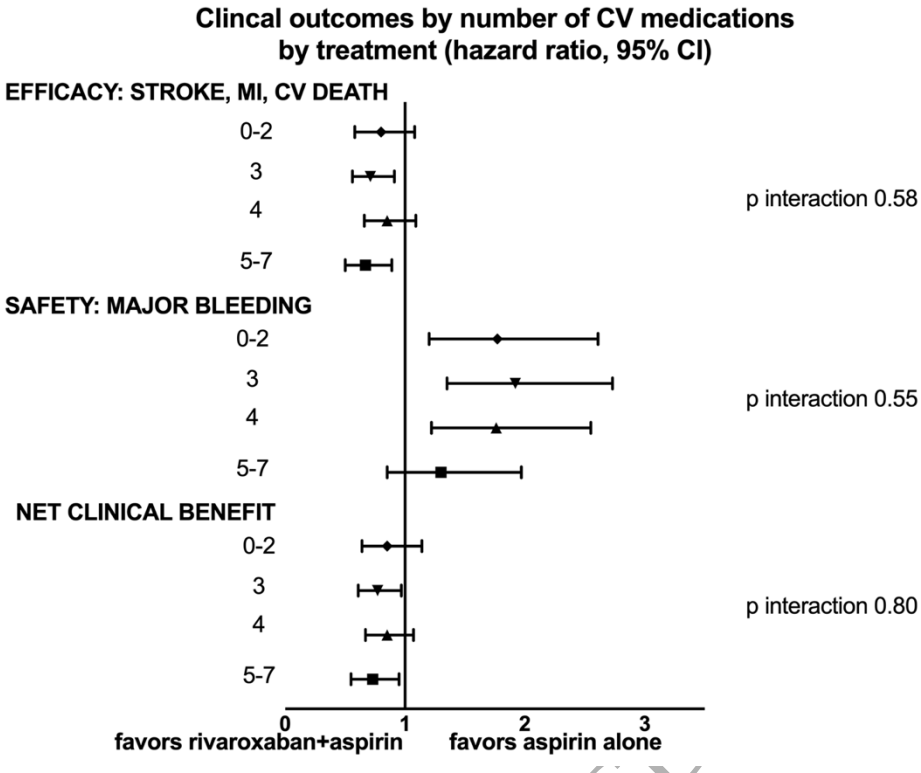


Figure 4. Effect of antithrombotic therapy by number of cardiovascular (CV) medications (A) and by number of comorbidities (B) (relative effect, hazard ratios and 95% CI)



A

B

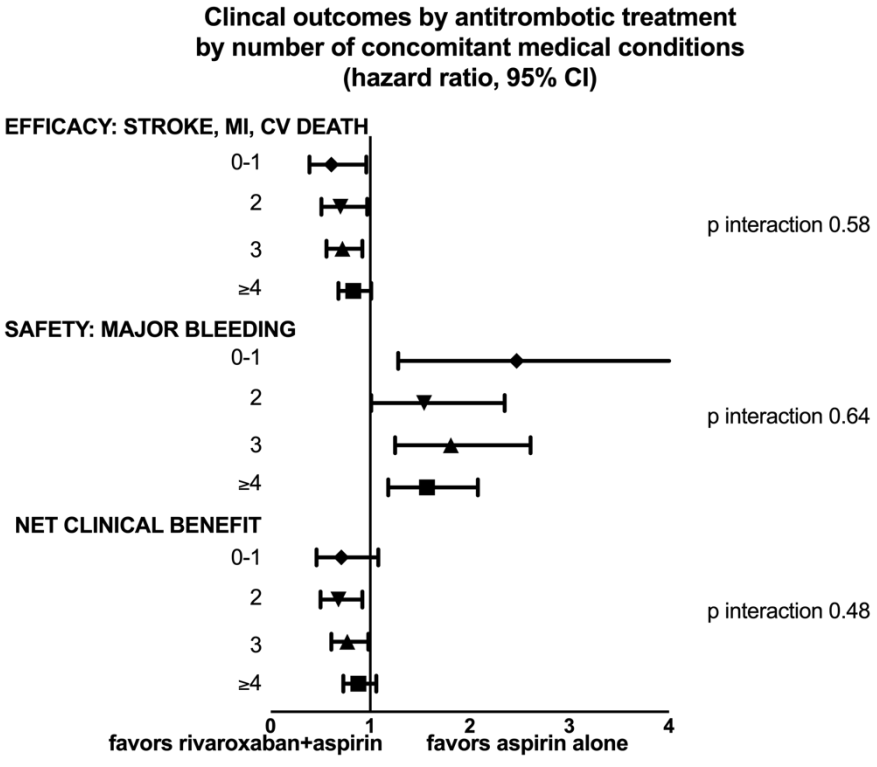


Figure 5. Absolute event rates by antithrombotic treatment by number of cardiovascular (CV) medications (A) and by number of comorbidities (B).