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FASTTRACK CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

External applicability of the COMPASS trial: an analysis of the reduction of atherothrombosis for continued health (REACH) registry

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Aims The aims of the present study were to describe the proportion of patients eligible for the COMPASS trial within the Reduction of Atherothrombosis for Continued Health (REACH) registry, the reasons for ineligibility, and to put in perspective the characteristics and outcomes of trial-eligible patients from the REACH registry compared with those of patients enrolled in the reference aspirin arm of the COMPASS trial.

Methods and results The COMPASS selection and exclusion criteria were applied to REACH patients with either coronary artery disease (CAD) or peripheral artery disease (PAD). We used the COMPASS primary composite outcome of cardiovascular (CV) death, myocardial infarction (MI), or stroke. In REACH, 31 873 patients had CAD or PAD and detailed information allowing evaluation of eligibility. Among these, 9518 (29.9%) patients had exclusion criteria and an additional 5480 patients (17.2%) did not fulfil the inclusion criteria and thus were not eligible. The 'COMPASS-Eligible' population therefore comprised 52.9% of the evaluable REACH patients ($n = 16\,875$). The main reasons for exclusion were high-bleeding risk (51.8%), anticoagulant use (44.8%), requirement for dual antiplatelet therapy within 1 year of an ACS or PCI with stent, (25.9%), history of ischaemic stroke <1 year (12.4%), and severe renal failure (2.2%). Eligibility was highest among patients with PAD alone (68.4%). COMPASS-Eligible patients from REACH experienced higher annualized primary outcome event rates than patients actually enrolled in the reference aspirin arm of COMPASS (4.2% vs. 2.9% per year, $P < 0.001$).

Conclusion COMPASS-Eligible patients represent a substantial fraction of stable CAD/PAD patients encountered in routine clinical practice in the large international REACH registry suggesting good external applicability. COMPASS-Eligible patients experienced a higher rate of the primary outcome compared with COMPASS participants in the aspirin alone treatment arm.

Keywords External applicability • COMPASS trial • REACH registry • Rivaroxaban • Coronary artery disease • Peripheral artery disease

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Introduction

Complications of atherothrombosis, encompassing coronary artery disease (CAD), peripheral artery disease (PAD), or cerebro-vascular disease (CVD), is a major public health issue as it represents the main cause of death worldwide.[1–3] Aspirin is the antithrombotic agent most widely used, for prevention of cardiovascular (CV) events, whether alone or associated with other antiplatelet agents.[4–6] However, due to a substantial residual ischaemic risk even in stable patients with atherothrombosis,[7–10] there have been efforts to develop more efficient antithrombotic strategies with either more potent antiplatelet therapy,[11,12] direct oral anticoagulants (DOAC),[13,14] or their combination. COMPASS[15] (ClinicalTrials.gov number, NCT01776424) was an international, randomized controlled trial (RCT), which showed a relative reduction of CV death, stroke, or myocardial infarction (MI) of 24% with a combination of rivaroxaban (2.5 mg b.i.d.) plus aspirin, compared with aspirin (100 mg o.d.), in patients with stable CAD or PAD.[16] The applicability of its results will therefore be of paramount importance in defining the optimal antithrombotic therapy in stable patients with CAD or PAD.

However, a common problem in translating the evidence acquired from RCTs to clinical practice is the issue of applicability of trial results, in particular the proportion of patients who would qualify for treatment, without taking into account affordability and availability (i.e. access issues).[17,18] It is often perceived that RCTs enrol highly selected trial participants who may substantially differ in terms of clinical characteristics, management, and outcomes from those encountered in routine clinical practice.[19] Therefore, it is important to assess the applicability of the COMPASS trial population compared with the entire spectrum of CAD and PAD patients.[20] Using the large international observational Reduction of Atherothrombosis for Continued Health (REACH) registry of patients at risk for or with established atherothrombosis, we set out to describe the proportion of COMPASS-Eligible patients among patients with CAD or PAD. Additional goals were to describe the reasons for ineligibility, and to compare the clinical characteristics, management and outcomes of COMPASS-Eligible REACH patients to those of actual COMPASS trial participants, using patients in the 'reference' aspirin arm of the trial.

Methods

COMPASS trial design

The COMPASS trial design has been previously published.[15] Briefly, COMPASS is a phase-3 RCT, which aimed to compare three antithrombotic strategies in stable CAD and PAD patients: aspirin 100 mg o.d., a combination of rivaroxaban 2.5 mg b.i.d. and aspirin 100 mg o.d., or rivaroxaban 5 mg b.i.d.

Stable CAD was defined in COMPASS as previous MI within the last 20 years or history of stable or unstable angina with evidence of multivessel coronary disease, or multivessel revascularization, either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

Stable PAD was defined as history of intermittent claudication with objective evidence of arterial disease (ankle/arm blood pressure ratio <0.9 or peripheral artery stenosis ≥50% documented by angiography or duplex ultrasound), previous limb or foot amputation for vascular disease, history of inferior limb revascularization (either by surgery of percutaneous transluminal angioplasty), and previous carotid revascularization or asymptomatic carotid disease with at least 50% stenosis. The detailed COMPASS inclusion and exclusion criteria are described in Supplementary material online, *Table S1*.

The primary outcome was the composite of CV death, stroke, or MI and occurred in 4.1% of patients of the rivaroxaban-plus-aspirin group, vs. 5.4% in the aspirin alone group [hazard ratio 0.76, 95% confidence interval (95% CI) 0.66–0.86].

The REACH registry

We used the REACH Registry database. The design of REACH has been previously described.[21] Briefly, REACH was a large prospective, observational, international registry of patients at least 45 years old, with either established atherosclerotic disease (CAD, PAD, or CVD) or with at least three atherosclerotic risk factors. Detailed selection criteria are provided in the Supplementary material online, *Table S2*.

Documented CAD was defined by a previous history of at least one of the following: stable angina, unstable angina, MI, or coronary revascularization, either by coronary angioplasty/stenting or CABG.

Documented PAD was defined as one or more of the following: history or current intermittent claudication with ankle-brachial index of less than 0.9, lower-limb artery angioplasty, stenting, or peripheral artery bypass graft, or previous amputation affecting lower limb. More than 65 000 outpatients from 44 countries were included from December 2003 until June 2004, in North America, Latin America, Europe, Middle East, Asia, and Australia. Every patient included in the REACH registry provided informed consent, and the protocol was approved by institutional review boards.

'COMPASS-Eligible' study population

In order to approximate the COMPASS trial population in REACH, patients from the REACH registry enrolled on the sole basis of having either CVD alone or only atherothrombotic risk factors alone (except for patients with history of asymptomatic carotid stenosis, or carotid angioplasty/surgery) were excluded, defining the PAD or CAD patient cohort in the REACH registry. In a second step, we excluded patients in whom detailed information regarding eligibility in COMPASS was incomplete or missing, therefore yielding a 'COMPASS-Evaluable' cohort with CAD or PAD, which is the study population for the present analyses.

The main COMPASS inclusion and exclusion criteria[15] were applied to the 'COMPASS-Evaluable' population. A detailed list of the COMPASS selection criteria and the adjustments required for the analysis of the REACH cohort (due to differences between the two populations or in the information available) is described in Supplementary material online, *Table S3*. First, patients meeting any COMPASS exclusion criteria were excluded (the 'COMPASS Excluded' subset). The main exclusion criteria were as follows: patients with high bleeding risk were identified using the REACH bleeding risk score, and any patient with a score > 10,[22] (corresponding to a 2-year risk of serious bleeding of 2.76%) was excluded. In accordance with COMPASS exclusion criteria, patients with severe renal insufficiency (defined as an estimated glomerular filtration rate <15 mL/min using the Cockroft & Gault formula) and patients with a need for dual antiplatelet therapy (DAPT) (which we defined as prior ACS or PCI in the previous 12 months), other non-aspirin antiplatelet therapy or oral anticoagulant therapy (OAT) were excluded. Patients with a history of ischaemic stroke in the past year were also excluded from the analysis.

Then, patients were included in the 'COMPASS-Eligible' subset, if they fulfiled the following COMPASS inclusion criteria:

- Peripheral artery disease patients, following COMPASS definition, were eligible, regardless of age.

- Coronary artery disease patients had to be aged > 65 years
- If CAD patients were <65 years, they had to fulfil at least one additional 'enrichment' criterion:
  - Documented atherosclerosis or documented prior revascularization involving at least two vascular beds (i.e. CVD or abdominal aortic aneurysm)
  - Or, at least two additional risk factors among the following: current smoker, diabetes mellitus, estimated GFR < 60 mL/min, or non-lacunar ischaemic stroke >1 year, or heart failure.

In COMPASS, patients without exclusion criteria, but with only CAD < 65 years, and no enrichment criteria were not eligible for enrolment ('COMPASS Non Included' subset).

Primary and secondary outcomes

The primary outcome of COMPASS was the composite of CV death, MI, and stroke. We also analysed secondary outcomes that were available in both the REACH and COMPASS databases, including CV death, non-fatal MI, non-fatal stroke, all-cause mortality, bleeding, and hospitalization for heart failure. The definitions used for bleeding events were different in REACH and in COMPASS. The 'serious bleeding' definition used in the REACH registry, was defined as any bleeding requiring transfusion, or hospitalization for transfusion or any haemorrhagic stroke. COMPASS bleeding definition was a modification of the International Society on Thrombosis and Hemostasis (ISTH) criteria for major bleeding, and included fatal bleeding, symptomatic bleeding in a critical organ, bleeding into a surgical site requiring reoperation, and bleeding leading to hospitalization.

Statistical analysis

Baseline characteristics of the following subgroups are described using mean ± standard deviation for continuous variables and frequencies and percentages for categorical variables.

- COMPASS-Eligible population: fulfiling the inclusion and exclusion criteria
- COMPASS-Excluded population: with at least one exclusion criteria
- COMPASS Not Included: patients without exclusion criteria, with CAD, but aged < 65 years, and not fulfiling any of the enrichment criteria.

Continuous and categorical baseline variables were compared between REACH subgroups using ANOVA and χ^2 tests, respectively. All outcomes are described by Kaplan–Meier estimates at 4 years, with 95% CI, except 'serious bleeding' and 'heart failure', assessed by cumulative percentages at 4 years (95% CI), since the 'time to event' information was not available for these specific outcomes.

In order to allow statistical comparisons[23] between COMPASS trial participants and COMPASS-Eligible REACH participants, the baseline characteristics were compared by Student's *t* and χ^2 tests for continuous and categorical variables respectively, and outcomes were also expressed as incidence rates by 100 patients-year with 95% CI. Given the *post hoc* and descriptive nature of these analyses, no adjustment was made for multiple comparisons.

Results

'COMPASS-Eligible' population

Among the 65 531 patients enrolled in the REACH Registry, 21 052 were excluded because they had only CVD or risk factor and 12 606 patients because of missing information precluding detailed assessment of eligibility for COMPASS. The flow chart is represented in *Figure 1*.

The remaining 31 873 patients constituted the study population, with either CAD or PAD, and in whom eligibility for enrolment in the COMPASS trial was evaluable. Of these evaluable patients, 9518 (29.9%) were excluded because of presence of at least one exclusion criteria ('COMPASS Excluded') and an additional 5480 patients (17.2%) had CAD but none of the enrichment criteria (PAD alone was sufficient for enrolment). Therefore, 16 875 patients were truly 'COMPASS-Eligible' (52.9% of the evaluable cohort).

Among evaluable patients, the main reasons for exclusion from the analysis were high-bleeding risk in 4932 patients (51.8%), the need for DAPT (related to either ACS or PCI in the prior 12 months) in 2562 patients (25.9%), the need for OAT in 4268 patients (44.8%), history of ischaemic stroke in the past year in 1182 participants (12.4%), and severe renal failure (defined as eGFR < 15 mL/min) in 210 patients (2.2%) (*Figure 2*).

The baseline characteristics of the COMPASS-Eligible subset are reported in *Table 1*.

Baseline characteristics differences between COMPASS-Eligible and COMPASS participants

A total of 9126 patients were included in the COMPASS aspirin alone treatment arm. There were important differences in baseline characteristics (*Table 1*) regarding age, sex, history of previous stroke or TIA, or history of remote MI between the two populations. In particular, the rates of use of evidence-based secondary prevention medications at baseline, including aspirin, statin, beta-blocker, and angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), (prior to inclusion) were consistently higher among COMPASS participants. Based on the Recurrent Ischaemic Event risk and Bleeding risk scores, (*Table 1*) COMPASS participants had a higher risk profile than COMPASS-Eligible patients from REACH (12.1 ± 2.8 vs. 9.9 ± 2.4 and 8.5 ± 2.2 vs. 7.2 ± 1.7; $P < 0.001$, respectively).

Main cardiovascular outcomes in COMPASS-Eligible REACH patients, compared with COMPASS participants

As shown in *Table 2* and *Figure 3*, COMPASS-Eligible patients from REACH experienced a higher primary outcome event rate per 100 patients/year [4.2 (4.0—4.3) vs. 2.9 (2.6—3.2) $P < 0,0001$] than actual COMPASS participants, enrolled in the reference aspirin treatment arm. The rates (per 100 patient/years) of all-cause mortality [3.2 (3.1–3.4) vs. 2.2 (1.9–2.4), $P < 0,001$] or CV death [1.9 (1.8–2.1) vs. 1.2 (1.0–1.3); $P < 0.001$] were also higher among COMPASS-Eligible patients from REACH.

The annual rate of major bleeding was evaluated at 1% per year in the reference arm of COMPASS. This cannot be directly compared with the 1-year rate of serious bleeding in COMPASS-Eligible patients from REACH [0.9% (0.8–1.1)] since the definitions differ also markedly. The rate per 100 patient/years of hospitalization for heart failure was 1.1 (0.8–1.1) in COMPASS participants, compared with 3.5% (3.2–3.8) at 1 year among COMPASS-Eligible patients from REACH.

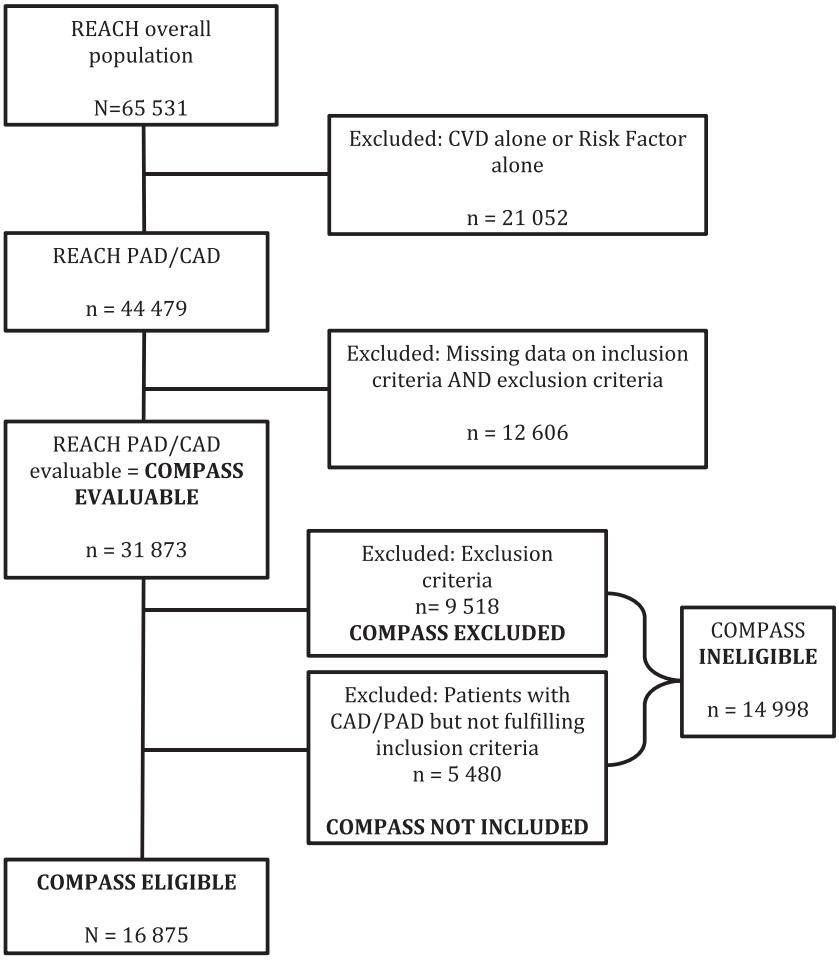

Figure 1 Flow chart for identification of COMPASS-Eligible population in REACH Registry.

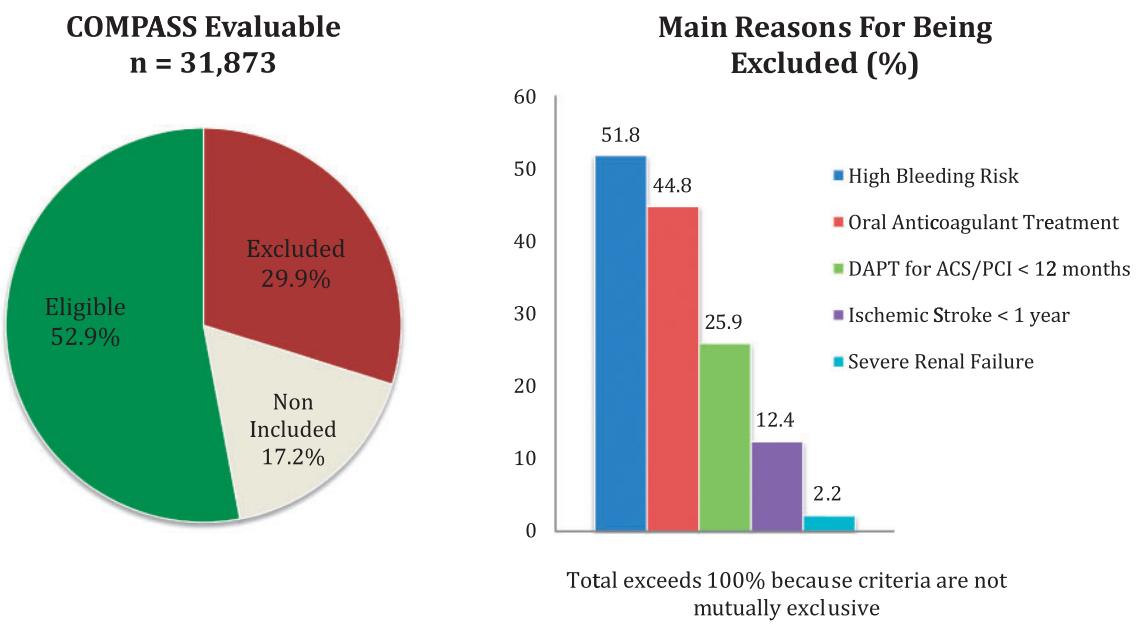

Figure 2 Proportion of COMPASS-Eligible, excluded and non-included patients in the REACH CAD/PAD evaluable population, and main reasons for exclusion. ACS, acute coronary syndrome; DAPT, dual anti platelet therapy; PCI, percutaneous coronary intervention.

Table 1 Baseline characteristics of patients included in the COMPASS-Eligible subset and aspirin alone treatment arm from COMPASS trial

	COMPASS-Eligible *n* = 16 875	COMPASS-Enrolled (aspirin alone arm) *n* = 9126	*P*-value for COMPASS eligible vs. enrolled
Age, mean (SD) (years)	71.1 (8.6)	68.2 (8.0)	<0.001
Age >75 years old, *n* (%)	5391 (31.9%)	1567 (17.2%)	<0.001
Body mass index, mean (SD)	27.9 (5.2)	28.4 (4.7)	<0.001
Male, *n* (%)	10 888 (64.5%)	7137 (78.2%)	<0.001
Medical history, *n* (%):			
Unstable angina	2686 (15.9%)	1689 (18.5%)	<0.001
Myocardial Infarction >1 year	6049 (35.8%)	5285 (57.9%)	<0.001
Coronary angioplasty/stenting	5457 (32.3%)	4905 (53.7%)	<0.001
Coronary artery bypass grafting	5039 (29.9%)	2143 (23.5%)	<0.001
Stroke/TIA >1 year	2646 (15.8%)	562 (6.1%)[a]	<0.001
Carotid revascularization[b]	1858 (11.1%)	N/A	N/A
Lower extremity revascularization[b]	1766 (10.5%)	674 (7.4%)	<0.001
Congestive heart failure[l]	2253 (13.5%)	1979 (21.7%)	<0.001
Serum creatinine (μmol/L) (SD)	96.8 ± 35.2	90.6 ± 25.0	<0.001
Hypertension	14 507 (86.0%)	6877 (75.4%)	<0.001
Hypercholesterolaemia	13 149 (78.0%)	N/A	N/A
Diabetes	6920 (41.0%)	3474 (38.1%)	0.031
Current smoker	2326 (13.9%)	1972 (21.6%)	<0.001
Risk score			
REACH recurrent ischaemic event risk score (SD)[c]	10.4 (2.7)	12.2 (2.8)	<0.001
REACH bleeding risk score (SD)[d]	7.4 (1.7)	8.5 (2.2)	<0.001
Baseline medications, *n* (%)			
Aspirin	13333 (79%)	7955 (87.1%)	<0.001
Other antiplatelet therapy	3580 (21.2%)	823 (9.0%)[e]	<0.001
Dual antiplatelet therapy	1794 (10.6%)	0 (0%)	<0.001
Statin[f]	12 719 (75.4%)	8158 (89.4%)	<0.001
Beta-blocker	9362 (55.6%)	6394 (70.0%)	<0.001
ACE-inhibitor or ARB	11 263 (66.8%)	6462 (70.8%)	<0.001

[a]Total of TIA and stroke from COMPASS trial. Mean years since TIA was 8.26 and 7.5 since last stroke.
[b]Includes angioplasty/stenting and surgical procedures.
[c]REACH ischaemic risk score ranges from 0 to > 29 and predict recurrent CV events in the REACH population. Each item in the score is assigned a number of points, Items used are: sex, age, smoking status, diabetes mellitus, body mass index, number of vascular beds with atherosthrombosis disease, CV event in past year, congestive heart failure, atrial fibrillation, statin therapy, aspirin therapy, and living country.
[d]REACH Bleeding Score uses several medical conditions to estimate a 2-year risk of serious bleeding in REACH registry population. Age, peripheral artery disease, chronic heart failure, diabetes mellitus, hypercholesterolaemia, hypertension, smoking, antiplatelet agents, and oral anticoagulants are assigned with a number of points. The score ranges from 0 to 23.
[e]Includes clopidogrel, ticagrelor, prasugrel, ticlopidine, and dipyridamole.
[f]Exact term in COMPASS trial is 'lipid lowering agent'.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MI, myocardial infarction; N/A, non-applicable; TIA, transient ischaemic attack.

The eligibility for the COMPASS trial according to the presence of CAD, PAD, or both and outcomes; their respective outcomes are reported in Supplementary material online, *Figures S2* and *S3* and *Table S6*.

Discussion

The present analysis shows that 'COMPASS-Eligible' patients represent a substantial fraction of the spectrum of stable CAD or PAD patients enrolled in a large international observational registry.

External applicability of randomized clinical trials in clinical practice is a major concern[17,18] and is often cited as a major reason for not applying evidence-based findings from randomized trials, since the rigorous selection criteria may result in enrolment of highly selected trial participants who may not reflect the characteristics and outcomes of patients encountered in routine clinical practice. In that regard, the COMPASS trial, despite having stringent selection criteria to identify a population able to tolerate combined antithrombotic therapy for several years, represents a substantial proportion of the spectrum of patients with CAD or PAD encountered in routine clinical practice. This eligibility rate (52.9%) may even be an

Table 2 Cardiovascular outcomes rates per 100 patients/year, for the 'COMPASS-Eligible' patients from REACH compared with actual, COMPASS trial participants (from the reference aspirin arm)

	COMPASS-Eligible in REACH (n = 16 875)	Actual COMPASS participants (aspirin reference arm) (n = 9126)	P-value
CV death, MI, or stroke	4.2 (4.0–4.3)	2.9 (2.6–3.2)	$P < 0.001$
All-cause mortality	3.2 (3.1–3.4)	2.2 (1.9–2.4)	$P < 0.001$
CV death	1.9 (1.8–2.1)	1.2 (1.0–1.3)	$P < 0.001$
Non-CV death	1.3 (1.2–1.4)	1.0 (0.9–1.2)	$P = 0.001$
Non-fatal MI	1.2 (1.1–1.3)	1.2 (1.0–1.4)[a]	N/A
Non-fatal stroke	1.3 (1.2–1.4)	0.8 (0.7–1.0)[a]	N/A

[a]Information regarding non-fatal MI or non-fatal stroke was not available in the COMPASS participants. COMPASS reported rates for combined 'fatal and non-fatal MI' and 'fatal and non-fatal stroke 'precluding direct comparisons between REACH and COMPASS for these outcomes.
CV, cardiovascular; MI, myocardial infarction;

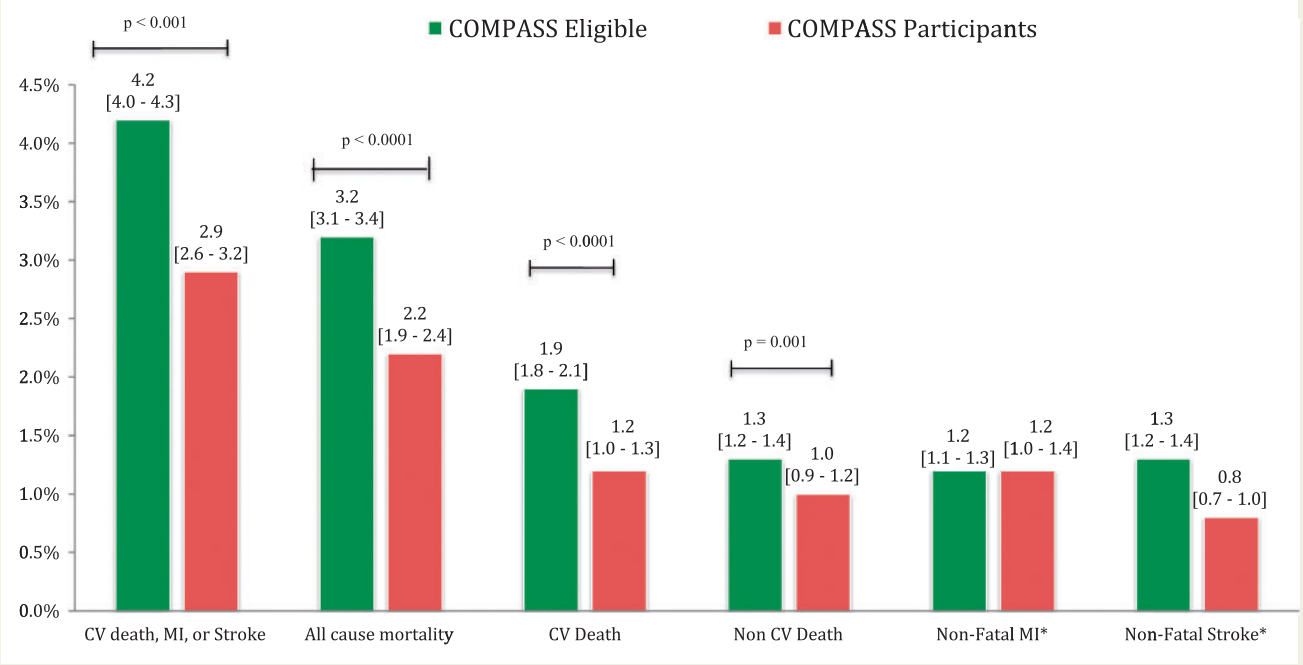

Figure 3 Comparison of main CV event rate per 100 patient/years for the COMPASS-Eligible subsets from REACH and COMPASS aspirin alone treatment arm (%)*: COMPASS only captured 'all MI' and 'all Stroke', whereas REACH captured non-fatal MI and non-fatal stroke, precluding direct statistical comparisons. CV, cardiovascular; MI, myocardial infarction.

underestimate of eligibility in daily clinical practice, considering the large number of patients (n = 4268, 44.8%) who were excluded solely on the basis of need for OAT. While these patients had to be excluded from the RCT, most would be eligible for treatment with rivaroxaban and aspirin if this combination was approved in this indication. Indeed, only patients with mechanical heart valve currently have a contraindication for DOAC and must receive vitamin K antagonists.

As previously shown[24,25] patients presenting with exclusion criteria precluding eligibility in randomized trials represent a high-risk subset with poor outcomes. Our findings confirmed this observation. Interestingly, current clinical trials aim to identify patients liable to derive benefit from addition of new treatments to the existing gamut of effective evidence-based secondary prevention drugs. In order to do so, 'enrichment' criteria are applied at the time of selection in order to find patients at slightly higher risk than the standard patients. Indeed, the observed annual rate of CV outcomes matched the severity predicted by baseline risk assessment in the three different subsets of the COMPASS Evaluable population (non-included, eligible, and excluded).

Baseline characteristics and management of REACH patients eligible for enrolment in COMPASS and those of actual COMPASS participants highlight some important differences between the two populations. First, we observed a mean difference of 3 years between the two subsets of patients, an absolute difference of 14% in the proportion of women, and a 2.5-fold higher rate of previous ischaemic

stroke and TIA in COMPASS-Eligible patients from REACH. In a population of stable atherosclerotic patients, these are of major importance and could account for, at least in part, the observed differences in CV outcomes between the two populations.[26] Secondly, the use of evidence-based medications and the rate of use of interventions were substantially higher in COMPASS participants, reflecting a population enrolled more recently and better treated than in REACH. The two studies were indeed conducted at two different time periods, while there have been significant changes in the therapeutic management of patients. In order to overcome this particular issue, we included a sensitivity analysis, focusing on optimally treated patients ($n = 4579$) (see Supplementary material online, *Table S5*), which we defined as non-smoker patients, treated with all four types of medications known to reduce the incidence of CV events in patients at very high risk of CVD, particularly in the context of secondary prevention (beta-blockers, ACE or ARBs, statins, and antiplatelet agents).[27] The rate of the primary outcome, expressed as 100-patients-year, in optimally treated patients was still higher compared with COMPASS participants [4.3 (3.9–4.7) vs. 2.9 (2.6–3.2)]. Overall, ischaemic outcomes appeared worse in REACH patients who were COMPASS-Eligible than in COMPASS-participants. This is to be expected as randomized long-term trials generally exclude people who are difficult to follow or are non-adherent.[28] Further, patients in trials have much closer follow-up than in clinical practice, which may improve their prognosis. Apart from the important multiple differences in baseline characteristics, there also were major differences in study design, geographic range and timing of enrolment, data capture, monitoring, and event adjudication between the two studies. For example, events were adjudicated in the COMPASS trial, but not in the REACH registry, and the adjudication process removed approximately 10% of outcome events in COMPASS. Because of these differences, comparisons across studies should be interpreted very conservatively and the unadjusted event rates are provided for descriptive purposes. The main goal of the present study was more to assess the eligibility for COMPASS in the REACH registry, than to compare formally outcome rates between the different groups.

Study strengths and limitations

The REACH registry provided a large, international representative sample of stable outpatients with atherothrombosis, with prolonged follow-up. However, there are some caveats to our observations. First, REACH patients were enrolled in 2003–04, more than a decade earlier than COMPASS patients, whereas there have been continuous improvements in the use of evidence-based therapies and in outcomes of patients with atherothrombosis. The differences observed in event rates between the registry and the more recent trial may therefore reflect intrinsic differences in baseline risk but also may reflect the substantial differences in the use and duration of secondary prevention medications, or to adherence to the latter.[27] Given the differences in design between an observational non-interventional registry and the standardized treatment regimen of a randomized trial, it is difficult to disentangle these factors, and differences should be interpreted with caution. Second, there were differences in the way clinical characteristics were defined or captured in REACH and in COMPASS and this required some adjustment of the COMPASS eligibility criteria used to study the REACH cohort: the definition of CAD used in the COMPASS trial required patients had to have at least one of the following: MI within 20 years, multi-vessel CAD, history of stable or unstable angina, or prior multi-vessel PCI, or prior multi-vessel CABG surgery. Thus, only patients with stable multivessel CAD (defined as stenosis of at least 50% of diameter in two or more coronary arteries, confirmed by coronary angiography, by non-invasive imaging or by stress studies suggesting significant ischaemia in two or more coronary artery territories) were included in COMPASS. The number of vessels treated during prior PCI or CABG, as well as the extent of CAD (multivessel vs. single vessel) was not captured in the REACH registry case record forms. Therefore, the lack of information regarding the extent of CAD in the REACH Registry may have overestimated the true eligibility in COMPASS. Conversely, since some patients with single-vessel disease were included in our analyses, we may have underestimated the rates of CV outcomes in the REACH population. An important exclusion criterion in COMPASS was the existence of a high bleeding risk (based on investigator judgement). This information was not prospectively captured in REACH, but we were able to assess bleeding risk formally and quantitatively by applying the REACH bleeding risk score[22] to our cohort and elected to exclude patients with a score >10, which represents a substantial risk (yearly risk of serious bleeding of 1.36%). Thus, the lower average bleeding risk in REACH patients compared with COMPASS participants may reflect an overly conservative selection process, underestimating COMPASS trial eligibility. In addition, the definition of serious bleeding used in REACH (which includes haemorrhagic stroke, hospitalization for bleeding, and transfusion) was very different from the modified ISTH definition of major bleeding used in COMPASS and precludes direct comparisons across studies, and therefore it is not possible to make any comparison of net clinical benefit between the two settings of REACH and COMPASS. Finally and importantly, criteria used to define eligibility in a clinical trial may not necessarily be the best criteria to define the optimal treatment population in routine clinical practice, and the generalizability of trial results is not solely related to the proportion of patients who met inclusion and exclusion criteria but also should include patients who could have benefitted from the medication tested but were already on it (e.g. patients already receiving anticoagulants who were excluded from COMPASS), and should take into account adherence, access, and affordability as well as the setting, which influences competing demands and considerations. For example, trial results may be more easily applicable to patients from Western Europe and North America than to Africa or South Asia where costs of the drugs are high relative to income at present.

Conclusions

Although there remain important differences between the two cohorts, the first being a recent randomized control trial and the second an observational registry conducted more than 10 years ago, COMPASS-Eligible patients represent a substantial fraction of the spectrum of the stable CAD/PAD outpatients from the REACH

registry. This population appeared at higher risk of ischaemic events than actual COMPASS participants.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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