



HAL
open science

Clinical characteristics and outcomes of COMPASS eligible patients in France. An analysis from the REACH Registry

A. Darmon, Y. Elbez, D.L. Bhatt, J. Abtan, J.L. Mas, P. Cacoub, G. Montalescot, I. Billaut-Laden, G. Ducrocq, P.G. Steg

► To cite this version:

A. Darmon, Y. Elbez, D.L. Bhatt, J. Abtan, J.L. Mas, et al.. Clinical characteristics and outcomes of COMPASS eligible patients in France. An analysis from the REACH Registry. *Annales de Cardiologie et d'Angéiologie*, 2020, 69, pp.158 - 166. 10.1016/j.ancard.2020.07.002 . hal-03492815

HAL Id: hal-03492815

<https://hal.science/hal-03492815>

Submitted on 17 Oct 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Clinical characteristics and outcomes of COMPASS eligible patients in France

An Analysis from the REACH Registry

Caractéristiques cliniques et pronostic des patients éligibles à COMPASS en France

Une analyse du registre REACH

Arthur Darmon¹, Yedid Elbez¹, Deepak L.Bhatt², Jérémie Abtan¹, Jean Louis Mas³, Patrice
Cacoub^{4,5,6,7}, Gilles Montalescot⁸, Ingrid Billaut-Laden⁹
Gregory Ducrocq^{1, 10} and Philippe Gabriel Steg^{1,10,11}

AFFILIATIONS

¹ FACT, French Alliance for Cardiovascular Trials, Département Hospitalo-Universitaire FIRE, Hôpital Bichat, Assistance Publique – Hôpitaux de Paris, Paris, France

² Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, USA

³ Department of Neurology, Sainte-Anne Hospital, Paris Descartes University, Inserm U1266, Paris

⁴ Sorbonne Universités, UPMC Université Paris 06, UMR 7211, and Inflammation-Immunopathology-Biotherapy Department (DHU i2B), F-75005, Paris, France;

⁵ INSERM, UMR_S 959, F-75013, Paris, France;

⁶ CNRS, FRE3632, F-75005, Paris, France;

⁷ AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, F-75013, Paris, France;

⁸ Sorbonne Université, ACTION Study Group, INSERM UMRS 1166, Institut de Cardiologie, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France

⁹ Bayer Healthcare SAS, Loos, France

¹⁰ INSERM U1148, LVTS, Paris, France

¹¹ Imperial College, Royal Brompton Hospital, London, United Kingdom

A complete list of the REACH Registry Investigators appears in Bhatt DL, Steg PG, Ohman EM, et al. JAMA. 2006;295:180-189.

Corresponding author: Gregory Ducrocq, Cardiology department Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France. Telephone: +33 1 40 25 86 68. Fax: +33 1 40 25 88 65.
Email: gregory.ducrocq@aphp.fr

Word Count: 2.907

Keywords: External applicability, COMPASS trial, rivaroxaban, coronary artery disease, peripheral arterial disease

Mots clefs : Applicabilité externe, essai COMPASS, rivaroxaban, maladie coronaire, maladie artérielle périphérique.

ABSTRACT

Background:

Following the publication of the COMPASS trial, the European Medicines Agency has approved a regimen of combination of rivaroxaban 2.5 mg twice daily and a daily dose of 75-100mg acetylsalicylic acid (ASA) for patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischemic events. However, the applicability of such a therapeutic strategy in France is currently unknown.

Aims:

To describe the proportion of patients eligible to COMPASS in France, their baseline clinical characteristics and the rate of major adverse cardiovascular events, using the REACH registry.

Methods

From the the REduction of Atherothrombosis for Continued Health (REACH) registry database, a large international registry of patients with, or at risk, of atherothrombosis, we analyzed patients included in France with either established CAD and/or PAD and fulfilling the inclusion and exclusion criteria of the COMPASS trial. The ischemic outcome was a composite of cardiovascular (CV) death, myocardial infarction (MI), or stroke, and serious bleeding were defined as haemorrhagic stroke or bleeding leading to hospitalization or transfusion.

Results

Among more than 65000 patients enrolled in REACH, 2.012 patients were evaluable and enrolled in France. Among them, 1194 patients (59.3%) were eligible to COMPASS. The

main reasons for exclusion of the COMPASS trial, were high bleeding risk (59.1%), anticoagulant use (43.4%), requirement for dual antiplatelet therapy within 1 year of an ACS or PCI (24.7%). In the “COMPASS eligible population”, the rate of MACE (CV, MI and stroke) at 4 years follow-up was 13.4% [11.3 – 15.8], and serious bleeding was 2.5% at 4 years [1.6 – 3.4]. Patients with polyvascular disease (n = 219) had the highest rate of MACE, compared with patients with CAD only and PAD only (19.1% [13.9 – 26.1] vs. 11.6% [9.1 – 14.8] vs 13.2% [9.2 – 18.8], $p < 0.0001$, respectively).

Conclusion

The COMPASS therapeutic strategy in France appears to be applicable to more than half of CAD or PAD patients. This population appears at high residual risk of atherothrombotic events, and patients with polyvascular disease experienced the highest rate of events.

RESUME

Contexte :

Suite à la publication de l'essai COMPASS, l'Agence Européenne du Médicament a approuvé l'association de rivaroxaban 2,5 mg deux fois par jour et d'aspirine 75 à 100 mg par jour pour les patients atteints de maladie coronaire chronique (MCC) ou de maladie artérielle périphérique (MAP) à haut risque d'événements ischémiques. Cependant, l'applicabilité d'une telle stratégie thérapeutique en France est actuellement inconnue.

Objectif :

Décrire la proportion de patients éligibles à COMPASS en France, leurs caractéristiques cliniques de base et le taux d'événements cardiovasculaires majeurs, au sein du registre REACH.

Méthodes

À partir du registre REACH, un registre international de patients atteints ou à risque d'athérombose, nous avons analysé les patients inclus en France avec une MCC et/ou une MAP remplissant les critères d'inclusion et d'exclusion de l'essai COMPASS. Le critère de jugement des événements ischémiques était un critère composite de décès cardiovasculaire (CV), d'infarctus du myocarde (IDM) ou d'accident vasculaire cérébral (AVC). Les saignements graves étaient définis comme un accident vasculaire cérébral hémorragique ou un saignement entraînant une hospitalisation ou une transfusion.

Résultats

Parmi plus de 65.000 patients inclus dans REACH, 2.012 patients étaient évaluables et inclus en France. Parmi eux, 1194 patients (59,3%) étaient éligibles à COMPASS. Les principales raisons d'exclusion de l'essai COMPASS étaient un risque hémorragique élevé (59,1%), l'utilisation d'anticoagulants (43,4%) et une double thérapie en raison d'un IDM < 12 mois (24,7%). Dans la population « COMPASS-Eligible», le taux d'évènement ischémique (décès CV, IDM et AVC) à 4 ans de suivi était de 13,4% [11,3 - 15,8], et les saignements graves étaient de 2,5% à 4 ans [1,6 - 3,4]. Les patients atteints de maladie polyvasculaire (n = 219) avaient le taux le plus élevé d'évènements, par rapport aux patients avec MCS uniquement et MAP uniquement (19,1% [13,9 - 26,1] vs 11,6% [9,1 - 14,8] vs 13,2% [9,2 - 18,8], p <0,0001, respectivement).

Conclusion

La stratégie thérapeutique COMPASS semble applicable à plus de la moitié des patients coronariens et/ou artéritiques en France. Cette population semble présenter un risque résiduel élevé d'évènements athérotrombotiques, et les patients atteints de maladie polyvasculaire ont le taux d'évènements le plus élevé.

INTRODUCTION

Atherothrombosis and its complications are the main causes of mortality on a worldwide scale(1, 2). In France, cardiovascular disease represents the main cause of death among women (27.2% of all death), and the second cause among men (23.0% of all death), after cancer(3). In order to lower the risk of adverse cardiovascular events in these patients, various strategies have been evaluated in order to improve antithrombotic therapy(4-9). Recently, based on the results of the COMPASS trial(10), the EMA has approved a regimen of rivaroxaban 2.5 mg twice daily plus acetylsalicylic acid (ASA) 75-100 mg once daily for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral arterial disease (PAD) at high risk for ischemic events. The applicability of the COMPASS trial has been previously evaluated globally, in the large REduction of Atherothrombosis for Continued Health Registry (REACH) with more than 65.000 patients with or at risk for atheromobosis. From the 31.873 patients that would have evaluable for inclusion in the COMPASS Trial, more than half (n=16.875, 52.9%) would have been eligible for COMPASS, suggesting good external applicability of such a strategy in routine clinical practice(11).

However, data available to characterize and to estimate the number of French patients fulfilling the COMPASS eligibility criteria are limited. The objectives of the present study were to evaluate the applicability of the COMPASS trial in France, describe demographic, clinical characteristics and rate of outcomes of the overall COMPASS-Eligible population in France, and in various clinically relevant subgroups of this population.

METHODS

The REACH registry

For the purpose of this study we used the REduction of Atherothrombosis for Continued Health (REACH) Registry database. The design of REACH has been previously described(12). Briefly, REACH was a large prospective, observational, international registry of patients aged at least 45 years old, with either established atherosclerotic disease (CAD, PAD, or cerebrovascular disease [CVD]) or with at least three atherosclerotic risk factors.

Documented CAD was defined by a previous history of at least one of the following: stable angina, unstable angina, myocardial infarction, 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. The definitions of CAD in REACH registry and COMPASS trial were similar, but asymptomatic carotid stenosis > 50% was defined as PAD in COMPASS (See **additional Table**).

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. After inclusion, patients were followed at 12 ± 3 months and 21 ± 3 months, and at yearly intervals for up to 4 years in selected countries. Every patient included in the REACH registry provided informed consent, and institutional review boards approved the protocol.

Identification of the COMPASS-Eligible population in France

The method used to identify the COMPASS-Eligible population within the REACH Registry has been previously published(11). Briefly, within the entire REACH cohort, we focused on the patients living in France. Then, we excluded, patients with CVD alone, patients with risk factors alone, or patients with missing data precluding precise assessment of COMPASS eligibility, in order to focus on a population with either CAD and/or PAD (“REACH – French Population”).

We applied the main exclusion criteria for COMPASS to the “**REACH – French Population**”: high bleeding risk evaluated using the REACH bleeding risk score(13) (patients with a score > 10, corresponding to a 2-year risk of serious bleeding of 2.76%), severe renal failure (estimated glomerular filtration rate (eGFR) < 15 mL/min), patients requiring dual antiplatelet therapy (DAPT) for an acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) less than 12 months ago, oral anticoagulant therapy and history of ischemic stroke in the past year. Then, we used the COMPASS inclusion criteria to identify the “REACH COMPASS – Eligible” population:

- PAD patients were eligible, whatever their age
- CAD patients aged > 65 years were also eligible
- CAD patients aged < 65 had to fulfil at least one additional “enrichment” criterion
 - o Documented atherosclerosis or documented prior revascularization involving at least two vascular beds
 - o Or, at least two additional risk factors defined by the COMPASS protocol: current smoker, diabetes mellitus, heart failure, estimated glomerular filtration rate (GFR) < 60 mL/min, or non-lacunar ischaemic stroke > 1 year.

Patients with CAD only aged < 65 years with no enrichment criteria were thus not eligible for COMPASS (“Non Included”).

Patients with at least one exclusion criterion (“Excluded”) and those without enrichment criteria (“Non Included”) were not eligible to COMPASS, and constituted the “REACH COMPASS Non Eligible” population.

The “**REACH COMPASS – Eligible**” population was divided into the following subgroups, according to vascular disease burden:

- CAD without PAD.
- PAD without CAD.
- CAD + PAD.

We also analyzed additional patient subsets of specific interest which had been prespecified for this analysis

- CAD patients (with or without PAD).
- PAD patients (with or without CAD).

Primary and secondary objectives

The primary objective of the present study was to estimate the proportion of patients eligible for COMPASS inclusion within the French subset of the REACH registry.

The secondary objectives were:

- To describe demographic and clinical characteristics of the overall “**REACH – COMPASS – Eligible**” population in France, and in the predefined different subgroups at baseline.
- Describe treatment patterns and changes during follow-up of patients within the “**REACH – COMPASS – Eligible**” population.

- To describe outcomes within the overall “**REACH – COMPASS Eligible**” population and in the various predefined subgroups.
 - o Ischaemic events analyzed were: the composite of CV death, MI or Stroke (COMPASS trial primary outcome), non-fatal MI, non fatal stroke, all cause death at 4 years follow-up
 - o Bleeding outcome analyzed was serious bleeding at 4 years follow-up. Serious bleeding was defined in REACH as any bleeding requiring hospitalization and/or transfusion or any haemorrhagic stroke.

Statistical analysis

All patient characteristics and treatment patterns at baseline and over time have been presented as sample size and percentage for categorical variables and mean and standard deviation for continuous variables. Clinical outcomes have been estimated with incidence rates at 4 years with a 95% confidence interval. Continuous and categorical baseline variables were compared between subgroups using ANOVA and Chi-square tests, respectively. Finally, Kaplan-Meier curves have been used to present the cumulative incidence rates by sub-populations according to CAD/PAD status.

RESULTS

Eligibility to the COMPASS trial in the REACH French population

The flow chart for identification of the “REACH COMPASS Eligible” population in France is presented in Figure 1. Among 65,531 patients enrolled in the REACH registry, 60,952 were excluded, as they were not living in France. Additionally, 1,545 patients with CVD alone (794) or with risk factors alone (751) were also excluded in order to identify a subset of patients with CAD and/or PAD. From the remaining 3,034 patients with CAD and/or PAD, 1,022 were excluded due to missing data regarding inclusion or exclusion criteria, precluding precise evaluation of the eligibility to COMPASS. The remaining patients constitute the “REACH – French population” (N = 2,012).

From the “REACH – French population”, 818 (40.6%) patients were not eligible to COMPASS because of the presence of at least 1 exclusion criterion for 574 (28.5%) patients or the absence of any of the enrichment criteria for 244 (12.1%) patients.

Eventually, 1194 patients were found to be COMPASS-eligible (“REACH – COMPASS – Eligible”), representing 59.3% of the evaluable “REACH – French population”.

The main reasons for exclusion of the COMPASS clinical trial, encountered within the “excluded” population were as follows:

- High Bleeding risk N = 339 (59.1%).
- Need for oral anticoagulant treatment: N = 249 (43.4%).
- DAPT for ACS or PCI < 12 months: N = 142 (24.7%).
- Ischemic stroke < 1 year: N = 28 (4.9%).
- Severe renal failure (eGFR < 15 mL/min): N = 5 (0.9%).

Baseline characteristics of the “REACH – COMPASS – Eligible” population and of predefined subgroups

Patients included in the “REACH – COMPASS – Eligible” population had a mean age of 71.2 years, and were mostly male (74.5%). Regarding past medical history, only few patients (5.5%) had a previous history of ischaemic stroke, 11.5% had a prior history of unstable angina, and 39.9% stable angina. 34.8% had had myocardial revascularization by PCI and 19.9% by CABG. The distribution of vascular disease burden was as follows: a majority (57.4%, n = 685) had CAD only (i.e. without associated CVD or PAD), 24.3% (n = 290) had PAD only, and patients with polyvascular disease represented 18.3% (n = 219) of the “REACH – COMPASS – Eligible” population. The most prevalent cardiovascular risk factor among the population was hypertension (80.5%), while diabetes represented 33.9% and current smoking only 13.1% of the population (46.9% were former smokers). Finally, there were very high rates of use of antiplatelet agents (90.5% with 63.9% under ASA) and lipid lowering drugs (84.1%). Other evidence-based secondary prevention therapies were less frequently prescribed, with 50.1% rate of beta-blockers, 38.8% of ACE inhibitors, and 22.3% of angiotensin II receptor antagonists (Table 1)

Compared with the other subsets of patients, patients with CAD only were older than patients with PAD only or patients with both CAD + PAD (73.2 vs. 68.4 and 68.6 years, respectively, $p < 0.05$), and included a higher proportion of women than the others two subsets. However patients with polyvascular disease had the highest rate of previous ischaemic stroke (16.0% vs 6.9% for PAD patients only and 3.9% for CAD patients only, $p < 0.05$).

Outcomes of the “REACH – COMPASS – Eligible” population and of predefined subgroups

The rate of CV death, MI or stroke was 13.4% [11.3 – 15.8] for the “REACH – COMPASS - Eligible” population (see **Table 2**). Other adverse cardiac events for the “REACH – COMPASS - Eligible” population including all-cause mortality (11.2% [9.3 – 13.4]) and CV death (7.0% [5.5 – 8.9]) are reported in **Table 2**.

Figure 2 represents the incidence of CV death, MI, or stroke according to the presence or absence of CAD or PAD, during 4 years follow up. In each of the subgroups, the event rate appeared linear along follow-up. However, the subset of patients with CAD and PAD had a higher rate of CV death, MI or stroke, compared to patients with CAD only and PAD only (19.1% [13.9 – 26.1] vs. 11.6% [9.1 – 14.8] and 13.2% [9.2 – 18.8], $p < 0.0001$ respectively) (**Table 2**). Moreover, this subgroup of polyvascular patients experienced a higher rate for each secondary outcome compared to other subsets of patients.

Serious bleeding rate, among the “REACH – COMPASS – Eligible” population was 2.5% [1.6 – 3.4] at 4 years follow-up. As seen with previous outcomes, the subset of patients with polyvascular disease had the highest rate of serious bleeding compared to other subsets (3.2% [0.9 – 5.5]).

Occurrence of treatment patterns changes during follow up, for the “REACH – COMPASS Eligible” population and predefined subgroups

The occurrence of treatment patterns changes during follow-up is described in Table 3. For the overall “REACH – COMPASS – Eligible” population, there were few changes in the treatment of these patients. However, at 1 year, 2.9% had developed an indication for oral anticoagulation, and 6.6% at 4 years. These patients, in daily life practice, would no longer be eligible for COMPASS.

DISCUSSION

The present analysis shows that the majority of chronic patients affected with CAD and/or PAD, in France, would be eligible for the addition of low dose rivaroxaban (2.5 mg twice daily) to their treatment regimen. According to the COMPASS inclusion and exclusion criteria, approximately 60% of the French CAD or PAD population would have been eligible. Conversely, approximately one out of four patients presented with exclusion criteria, mainly related to high bleeding risk, and approximately one in ten patients were not at high enough ischemic risk to justify addition of low dose rivaroxaban. This eligibility rate among French REACH patients is slightly higher than in the entire REACH population, where 52.9% of the population was eligible, (11) and in the FAST-MI Registry, where 44% of the patients were eligible(14). However, the population included in the FAST-MI Registry was slightly different from the COMPASS Trial, as it recruited patients following an acute myocardial infarction, rather than patients with either chronic coronary syndromes or PAD. The proportion of patients excluded was almost similar (29.9% vs. 28.5% in the French population), but the rate of patients without enrichment criteria was higher (17.2% vs. 12.1% in the French population).

The baseline characteristics of the patients included in the “REACH – COMPASS – Eligible” population were consistent with the literature. Regarding chronic CAD outpatients, the baseline characteristics of CORONOR patients(15) (4,184 French patients from the region “Hauts-de-France” enrolled from February 2010 to April 2011) and of CLARIFY(16) (2,432 French patients enrolled between November 2009 and July 2010) were similar to those from the “REACH – COMPASS – Eligible” population. Regarding PAD patients, baseline characteristics from patients enrolled in COPART(17) (a French registry of 940 hospitalized patients with PAD) are relatively similar with those from the “REACH – COMPASS – Eligible” population. Thus, these descriptive data provide a good insight into a chronic vascular population in current daily practice.

A large majority of “**REACH – COMPASS – Eligible**” patients had CAD (75.7%) as in the COMPASS trial population(10) (90.6%). However, PAD patients represented 42.6% of the population, compared with 27.2% in the COMPASS trial.

Overall, use of evidence-based secondary prevention therapies was high and relatively stable throughout the study, although there was a steady accrual of new indications for oral anticoagulant therapy, and such patients would become ineligible for use of low dose rivaroxaban combined with aspirin.

The rate of the primary outcome for the French “**REACH – COMPASS - Eligible**” population (13.4% [11.3 - 15.8], corresponding to 3.7 [3.1 – 4.4] expressed as 100-patients year) was lower than in the international REACH registry COMPASS-Eligible population (4.2 [4.0 – 4.3], expressed as 100-patients year), but still higher than the actual COMPASS trial population included in the aspirin alone treatment arm (2.9 [2.6 – 3.2], expressed as 100-patients year). This could be explained by the fact that patients enrolled in large randomized controlled trials (RCT) are highly selected, closely managed, with a higher prescription rate of secondary prevention medications(11), and followed up with fixed scheduled visit for the

study duration. It has also been described that, with similar inclusion and exclusion criteria, patients actually included in RCTs have a better prognosis than trial eligible patients who are not actual RCT participants(18-20). As previously established (21-23), patients with both CAD and PAD presented the highest risk of ischemic outcomes, but also of serious bleeding at 4-year follow-up. Conversely, patients with “CAD only” had lower ischemic and bleeding risks. This is consistent with the fact that CAD only was not sufficient for eligibility in COMPASS, and CAD patients had to present enrichment criteria (such as older age or two cardiovascular risk factors) to be included in COMPASS.

There are limitations to this analysis.

The REACH registry enrolled patients between 2003 and 2004, whereas enrollment in COMPASS began in 2013. In ten years, the management and prognosis of these patients have substantially improved due to optimization of medical treatments and broader use of coronary revascularization when indicated.

A few COMPASS eligibility criteria were not collected as part of the REACH registry, and others were identified in the REACH database using a definition slightly different from the one used in the COMPASS trial. As an example, an important exclusion criterion in COMPASS was a high bleeding risk (based on investigator judgment). This information was not prospectively captured in REACH, but it was possible to assess bleeding risk formally and quantitatively by applying the REACH bleeding risk score to the cohort and excluding patients with a score > 10 , which represents a substantial risk (yearly risk of serious bleeding of 1.36%). High bleeding risk was the most reason for exclusion in the present analysis. Another threshold would have led to a difference in patients excluded, thus potentially changing the eligibility rate for COMPASS.

The definitions used in REACH and COMPASS for bleeding events differed. Serious bleeding in REACH was defined as a haemorrhagic stroke or any bleeding leading to hospitalization or transfusion. The definition used in COMPASS for major bleeding was a modified definition of the International Society of Thrombosis and Haemostasis (ISTH) including fatal bleeding, bleeding in a critical organ, leading to a surgical intervention or hospitalization. In that regard, no formal comparison between bleeding events between “REACH – COMPASS – Eligible” population and the actual COMPASS participants can be made. For descriptive purpose we reports here the annual rate of major bleeding was evaluated at 1% per year in the reference arm of COMPASS (10), and 2.5% [1.6 – 3.4] at 4 years follow-up for the “REACH – COMPASS – Eligible” population.

This analysis possibly includes a minority of patients on clopidogrel or other single antiplatelet therapy, and not aspirin, which have not been evaluated in COMPASS.

Finally, the French subset represented only 6.9% of the entire population included in the REACH registry, and the “REACH – COMPASS - Eligible population only 1.8%. Moreover, patients included in the subgroups analysis represented a small fraction of the entire “REACH –COMPASS - Eligible” population.

CONCLUSIONS

The COMPASS therapeutic strategy in France appears to be applicable to a substantial proportion of CAD and/or PAD patients, with more than half fulfilling trial selection criteria. This population appears at high residual risk of atherothrombotic events, and among the entire eligible population, patients with polyvascular disease experienced a higher rate of events.

FIGURES LEGEND

Figure 1: Flow chart for the identification of the “REACH COMPASS Eligible” population in France.

This flow chart represents the methodology we used in order to define the population eligible to COMPASS, in the French patients from the overall REACH Registry.

Figure 2: Kaplan-Meier curves for CV death, MI or stroke for the “REACH – COMPASS – Eligible” population according to PAD and/or CAD status

The overall “REACH COMPASS Eligible” was divided according to the vascular disease burden. Patients with PAD always have a higher risk of CV death, MI or stroke compared to patients with CAD, whether regarding patients with only one, one ± one additional, or two vascular bed diseased.

LEGENDES DES FIGURES

Figure 1: Organigramme d'identification de la population «REACH COMPASS Eligible» en France.

Cet organigramme représente la méthodologie que nous avons utilisée pour définir la population éligible à COMPASS, chez les patients inclus en France dans le registre REACH.

Figure 2: Courbes de Kaplan-Meier pour le critère composite décès CV, IDM ou AVC pour la population «REACH - COMPASS - Eligible» selon le statut MCC et/ou MAP

La population «REACH COMPASS Eligible» a été scindée en fonction du nombre de lits vasculaire atteints. Les patients atteints de MAP ont toujours un risque plus élevé de décès

cardiovasculaire, d'infarctus du myocarde ou d'accident vasculaire cérébral par rapport aux patients atteints de MCC, qu'il s'agisse de patients avec seulement un, un \pm un lit vasculaire supplémentaire atteint ou deux lits vasculaires malades.

Additional Table: Comparison of definition of chronic coronary artery disease and peripheral artery disease in the COMPASS trial and in the REACH registry

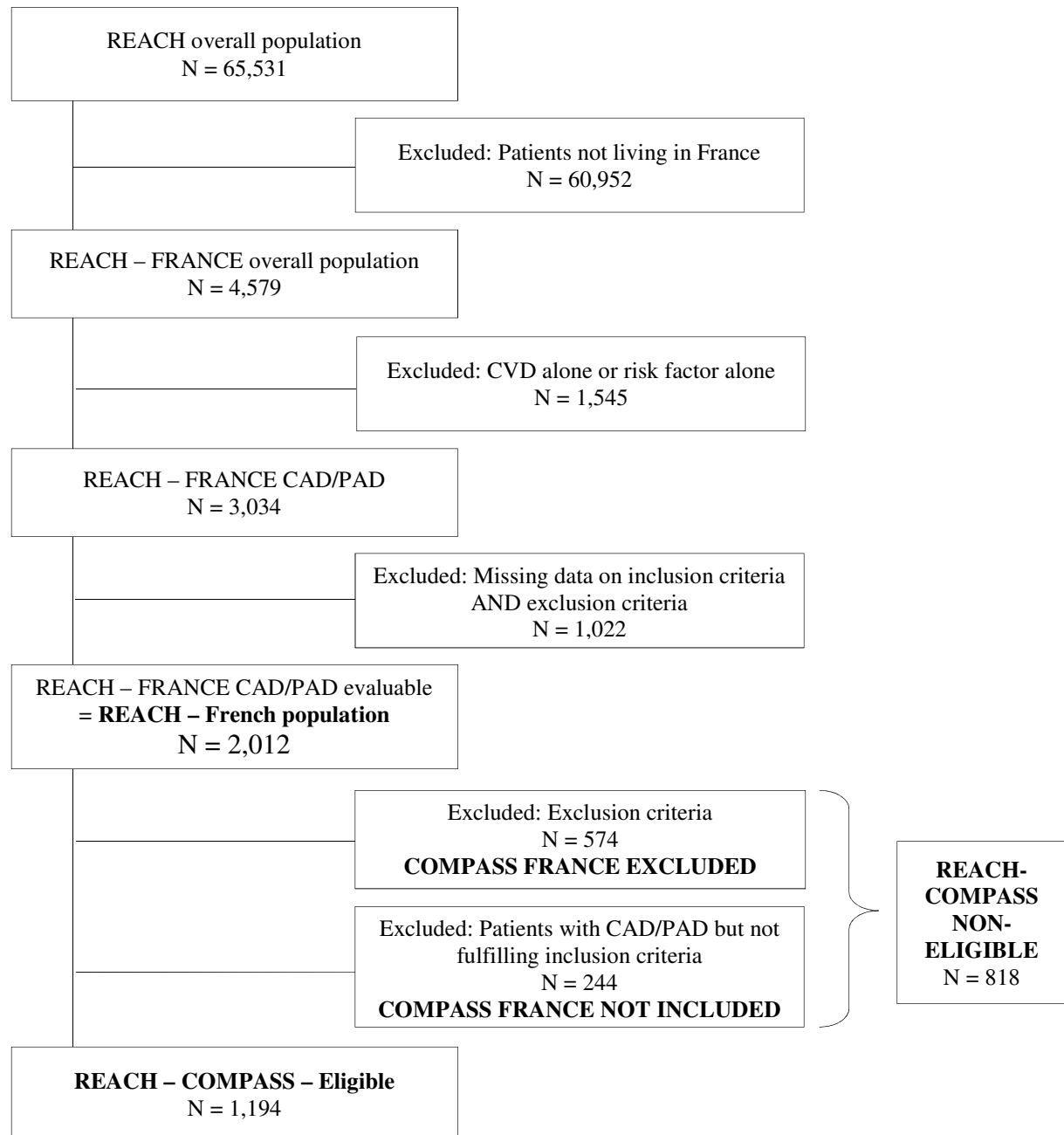
	COMPASS trial	REACH registry
Coronary Artery Disease	<p>Myocardial infarction within the last 20 years, or ≥ Multi-vessel coronary disease with symptoms or history of stable or unstable angina, or ≥ Multi-vessel percutaneous coronary intervention (PCI), or ≥ Multi-vessel CABG surgery</p> <p>Refers to stenosis of greater than or equal to 50% in two or more coronary arteries, confirmed by invasive coronary angiography, or non-invasive imaging or stress studies (e.g. exercise or pharmacologic) suggestive of significant ischemia in 2 or more coronary territories; or in 1 coronary territory if at least one other territory has been revascularized</p>	<p>One or more of the following</p> <ul style="list-style-type: none"> . Stable angina . Unstable angina . Myocardial infarction . Coronary revascularization, either by coronary angioplasty/stenting or CABG.
Peripheral Artery Disease	<ul style="list-style-type: none"> . Previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac, or infrainguinal arteries, or ≥ Previous limb or foot amputation for arterial vascular disease (i.e., excludes trauma), or ≥ History of intermittent claudication and one or more of the following: <ol style="list-style-type: none"> 1) an ankle/arm blood pressure (BP) ratio < 0.90, or 2) significant peripheral artery stenosis (≥50%) documented by angiography, or by duplex ultrasound, or ≥ Previous carotid revascularization (e.g., endarterectomy, stenting) or asymptomatic (i.e., no ipsilateral stroke or transient ischemic attack within 6 months) carotid artery stenosis ≥ 50% as diagnosed by duplex ultrasound or angiography. 	<p>One or more of the following:</p> <ul style="list-style-type: none"> . History or current intermittent claudication with ankle-brachial index of less than 0.9 . Lower-limb artery angioplasty / stenting . Peripheral artery bypass graft . Previous amputation affecting lower limb.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation*. 2015;131(4):e29-322.
2. Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe 2015: epidemiological update. *European heart journal*. 2015;36(40):2673-4.
3. Direction de la recherche dé, de l'évaluation et des statistiques. L'état de santé de la population en France - Rapport 2017. 2017.
4. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine*. 2009;361(11):1045-57.
5. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine*. 2007;357(20):2001-15.
6. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *The New England journal of medicine*. 2011;365(8):699-708.
7. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *The New England journal of medicine*. 2006;354(16):1706-17.
8. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *The New England journal of medicine*. 2012;366(1):9-19.
9. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. *The New England journal of medicine*. 2012;366(15):1404-13.
10. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *The New England journal of medicine*. 2017.
11. Darmon A, Bhatt DL, Elbez Y, Aboyans V, Anand S, Bosch J, et al. External applicability of the COMPASS trial: an analysis of the reduction of atherothrombosis for continued health (REACH) registry. *European heart journal*. 2018;39(9):750-7a.
12. Ohman EM, Bhatt DL, Steg PG, Goto S, Hirsch AT, Liao CS, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. *Am Heart J*. 2006;151(4):786 e1-10.
13. Ducrocq G, Wallace JS, Baron G, Ravaud P, Alberts MJ, Wilson PW, et al. Risk score to predict serious bleeding in stable outpatients with or at risk of atherothrombosis. *European heart journal*. 2010;31(10):1257-65.
14. Schiele F, Puymirat E, Ferrieres J, Simon T, Fox KAA, Eikelboom J, et al. The FAST-MI 2005-2010-2015 registries in the light of the COMPASS trial: The COMPASS criteria applied to a post-MI population. *International journal of cardiology*. 2019;278:7-13.
15. Bauters C, Deneve M, Tricot O, Meurice T, Lamblin N, Investigators C. Prognosis of patients with stable coronary artery disease (from the CORONOR study). *The American journal of cardiology*. 2014;113(7):1142-5.
16. Danchin N, Ferrieres J, Guenoun M, Cattan S, Rushton-Smith SK, Greenlaw N, et al. Management of outpatients in France with stable coronary artery disease. Findings from the prospective observational Longitudinal Registry of patients with stable coronary artery disease (CLARIFY) registry. *Arch Cardiovasc Dis*. 2014;107(8-9):452-61.

17. Cambou JP, Aboyans V, Constans J, Lacroix P, Dentans C, Bura A. Characteristics and outcome of patients hospitalised for lower extremity peripheral artery disease in France: the COPART Registry. *Eur J Vasc Endovasc Surg.* 2010;39(5):577-85.
18. Puymirat E, Schiele F, Zeller M, Jacquemin L, Leclercq F, Marcaggi X, et al. Do randomized clinical trial selection criteria reflect levels of risk as observed in a general population of acute myocardial infarction survivors? The PEGASUS trial in the light of the FAST-MI 2005 registry. *International journal of cardiology.* 2016;223:604-10.
19. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet.* 2005;365(9453):82-93.
20. Steg PG, Lopez-Sendon J, Lopez de Sa E, Goodman SG, Gore JM, Anderson FA, Jr., et al. External validity of clinical trials in acute myocardial infarction. *Arch Intern Med.* 2007;167(1):68-73.
21. Alberts MJ, Bhatt DL, Mas JL, Ohman EM, Hirsch AT, Rother J, et al. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. *European heart journal.* 2009;30(19):2318-26.
22. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA.* 2010;304(12):1350-7.
23. Chen DC, Singh GD, Armstrong EJ, Waldo SW, Laird JR, Amsterdam EA. Long-Term Comparative Outcomes of Patients With Peripheral Artery Disease With and Without Concomitant Coronary Artery Disease. *The American journal of cardiology.* 2017;119(8):1146-52.

Figure 1: Flow chart for the identification of the “REACH COMPASS Eligible” population in France.



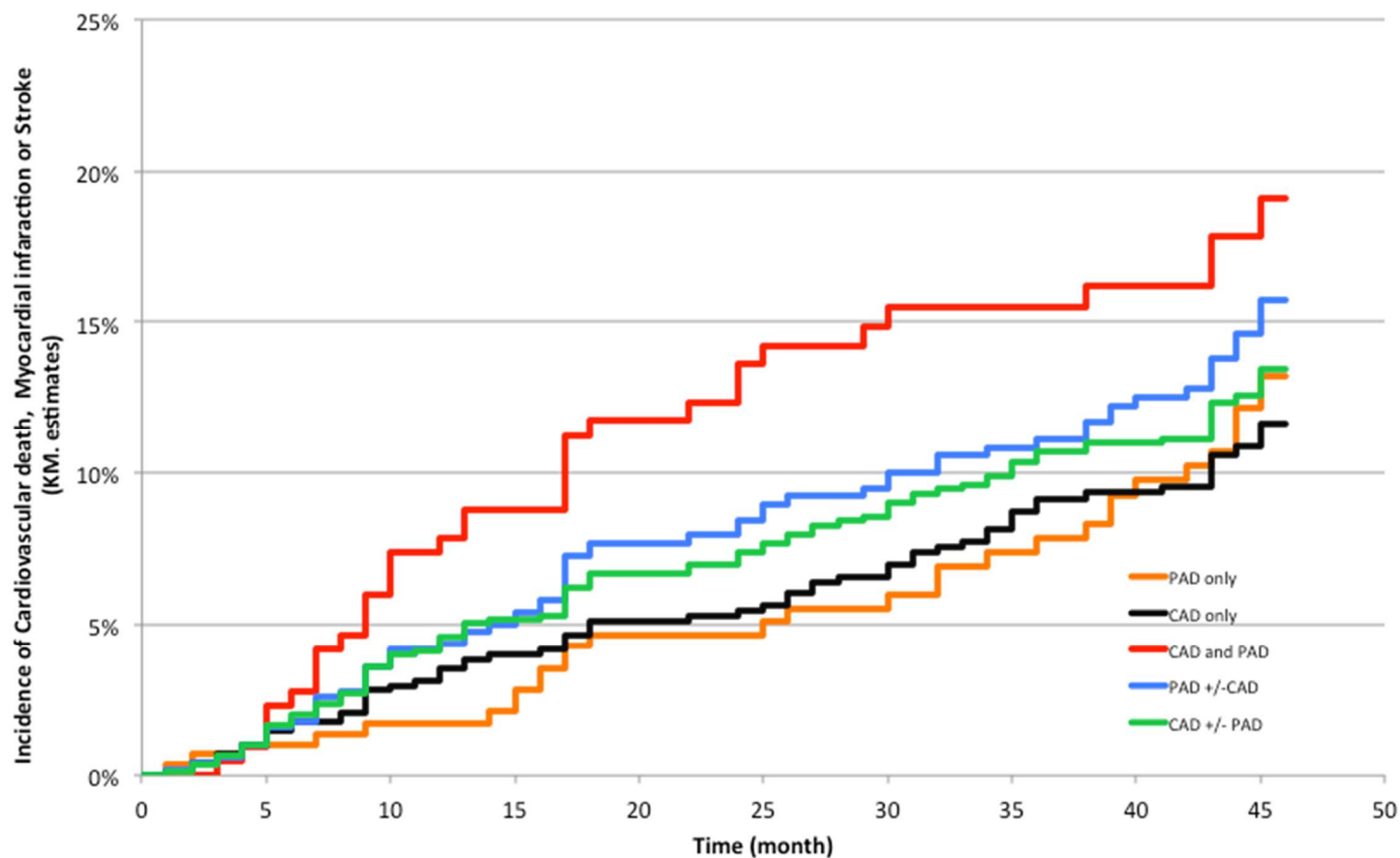
Abbreviations:

CAD: Coronary Artery Disease (Maladie coronaire chronique)

CVD: Cerebrovascular Disease (Maladie cérébrovasculaire)

PAD: Peripheral Artery Disease (Maladie artérielle périphérique)

Figure 2: Kaplan-Meier curves for CV death, MI or stroke for the “REACH – COMPASS – Eligible” population according to PAD and/or CAD status



Abbreviations : CAD : Coronary Artery Disease (Maladie coronaire chronique) CV : Cardiovascular (Cardiovasculaire), CVD : Cerebrovascular Disease (Maladie cerebro-vasculaire), MI : Myocardial Infarction (Infarctus du myocarde)

Table 1: Baseline characteristics of the “REACH – COMPASS - Eligible” population and subgroups according to CAD and/or PAD status

	REACH – COMPASS - Eligible N = 1194	REACH – COMPASS - Eligible CAD without PAD N = 685	REACH – COMPASS - Eligible PAD without CAD N = 290	REACH – COMPASS - Eligible CAD and PAD N = 219	p-value for subgroups comparison	REACH – COMPASS - Eligible CAD with or without PAD N = 904	REACH – COMPASS - Eligible PAD with or without CAD N = 509
<i>Demographics</i>							
Age (years), mean ± SD	71.19 (8.89)	73.21 (7.31)	68.36 (10.4)	68.63 (9.55)	0.0095	72.1 (8.14)	68.48 (10.03)
Age ≥ 75 years, n (%)	407 (34.1%)	271 (39.6%)	82 (28.3%)	54 (24.7%)	<0.0001	325 (36%)	136 (26.7%)
Male, n (%)	890 (74.5%)	474 (69.2%)	231 (79.7%)	185 (84.5%)	<0.0001	659 (72.9%)	416 (81.7%)
<i>Physical examination</i>							
Weight (kg), mean ± SD	76.85 (14.58)	76.4 (14.8)	75.89 (13.67)	79.53 (14.79)	<0.0001	77.16 (14.85)	77.46 (14.26)
Height (m), mean ± SD	1.67 (0.08)	1.66 (0.08)	1.68 (0.08)	1.69 (0.07)	<0.0001	1.67 (0.08)	1.68 (0.08)
Seated systolic blood pressure (mmHg), mean ± SD	138.22 (15.44)	136.99 (15.03)	141.82 (15.76)	137.35 (15.65)	<0.0001	137.08 (15.17)	139.89 (15.85)
Seated diastolic blood pressure (mmHg), mean ± SD	78.07 (8.58)	77.59 (8.42)	79.65 (8.41)	77.51 (9.07)	0.0016	77.57 (8.58)	78.73 (8.75)
<i>Available measurement</i>							
Serum creatinine (mg/dL), mean ± SD	1.08 (0.32)	1.05 (0.28)	1.09 (0.31)	1.15 (0.4)	<0.0001	1.08 (0.32)	1.12 (0.35)
eGFR (mL/min), mean ± SD	70.43 (27.17)	68.63 (25.46)	72.58 (29.24)	73.25 (29.12)	0.0273	69.75 (26.45)	72.87 (29.17)
<i>Medical history</i>							
Documented TIA, n (%)	100 (8.4%)	34 (5%)	41 (14.2%)	124 (56.9%)	<0.0001	476 (52.7%)	124 (24.4%)
Documented ischemic stroke, n (%)	66 (5.5%)	27 (3.9%)	20 (6.9%)	35 (16%)	0.0143	137 (15.2%)	35 (6.9%)
Stable angina, n (%)	476 (39.9%)	352 (51.4%)	0 (0%)	104 (47.5%)	<0.0001	451 (49.9%)	104 (20.4%)
Unstable angina, n (%)	137 (11.5%)	102 (14.9%)	0 (0%)	95 (43.4%)	<0.0001	415 (45.9%)	95 (18.7%)
Myocardial infarction, n (%)	451 (37.8%)	347 (50.7%)	0 (0%)	74 (33.8%)	<0.0001	237 (26.2%)	74 (14.6%)
Coronary angioplasty / stenting, n (%)	415 (34.8%)	320 (46.7%)	0 (0%)	124 (56.9%)	<0.0001	476 (52.7%)	124 (24.4%)
CABG, n (%)	237 (19.9%)	163 (23.8%)	0 (0%)	35 (16%)	<0.0001	137 (15.2%)	35 (6.9%)

Carotid angioplasty / stenting, n (%)	47 (3.9%)	0 (0%)	17 (5.9%)	30 (13.8%)	<0.0001	30 (3.3%)	47 (9.3%)
Carotid surgery, n (%)	99 (8.3%)	0 (0%)	54 (18.6%)	45 (20.6%)	<0.0001	45 (5%)	99 (19.5%)
Congestive heart failure, n (%)	50 (4.2%)	33 (4.9%)	3 (1%)	14 (6.5%)	N.A.	47 (5.3%)	17 (3.4%)
Atrial fibrillation / flutter*, n (%)	54 (4.6%)	36 (5.3%)	9 (3.1%)	9 (4.2%)	0.3220	45 (5%)	18 (3.6%)
Abdominal aortic aneurysm, n (%)	69 (6.2%)	24 (3.9%)	15 (5.5%)	30 (14.2%)	<0.0001	54 (6.5%)	45 (9.3%)
Asymptomatic carotid stenosis $\geq 70\%$ #, n (%)	107 (12.9%)	0 (0%)	55 (24.1%)	52 (29.4%)	<0.0001	52 (8.7%)	107 (26.4%)
Diabetes, n (%)	405 (33.9%)	241 (35.2%)	90 (31%)	74 (33.8%)	0.4570	315 (34.8%)	164 (32.2%)
Treated hypertension, n (%)	961 (80.5%)	537 (78.4%)	237 (81.7%)	187 (85.4%)	0.0626	724 (80.1%)	424 (83.3%)
Smoking status					<0.0001		
- Former, n (%)	556 (46.9%)	278 (40.6%)	144 (50.7%)	134 (62%)		412 (45.7%)	278 (55.6%)
- Current, n (%)	155 (13.1%)	60 (8.8%)	59 (20.8%)	36 (16.7%)		96 (10.7%)	95 (19%)
- Never, n (%)	474 (40%)	347 (50.7%)	81 (28.5%)	46 (21.3%)		393 (43.6%)	127 (25.4%)
Medications							
Antiplatelet agents, n (%)	1081 (90.5%)	623 (90.9%)	251 (86.6%)	207 (94.5%)	0.0084	830 (91.8%)	458 (90%)
Aspirin, n(%)	763 (63.9%)	506 (73.9%)	130 (44.8%)	127 (58%)	<.0001	633 (70%)	257 (50.5%)
Lipid lowering drugs, n (%)	1003 (84.1%)	585 (85.5%)	218 (75.2%)	200 (91.7%)	<0.0001	785 (87%)	418 (82.3%)
Beta-blockers, n (%)	598 (50.1%)	414 (60.4%)	65 (22.4%)	119 (54.3%)	<0.0001	533 (59%)	184 (36.1%)
Nitrates, n (%)	416 (35%)	296 (43.5%)	21 (7.3%)	99 (45.4%)	<0.0001	395 (43.9%)	120 (23.7%)
Diuretics, n (%)	510 (42.7%)	265 (38.7%)	154 (53.1%)	91 (41.6%)	0.0002	356 (39.4%)	245 (48.1%)
Angiotensin converting enzyme inhibitors, n (%)	463 (38.8%)	276 (40.4%)	94 (32.4%)	93 (42.5%)	0.0316	369 (40.9%)	187 (36.7%)
Angiotensin II receptor antagonists, n (%)	265 (22.3%)	140 (20.5%)	83 (28.6%)	42 (19.2%)	0.0102	182 (20.2%)	125 (24.6%)
Antidiabetic agents, n (%)	386 (32.3%)	230 (33.6%)	85 (29.3%)	71 (32.4%)	0.4282	301 (33.3%)	156 (30.6%)

* These patients were in AF, but have not been prescribed with any oral anticoagulation by their referent practitioner.

In COMPASS, the definition of asymptomatic carotid stenosis was $> 50\%$.

N.A.: Not applicable.

Table 2: Main cardiovascular outcomes rates at 4-years, for the “REACH – COMPASS - Eligible” population and subgroups according to CAD and/or PAD status

	REACH –COMPASS – Eligible Total N = 1,194	REACH – COMPASS - Eligible CAD without PAD N = 685	REACH – COMPASS - Eligible PAD without CAD N = 290	REACH – COMPASS - Eligible CAD and PAD N = 219	REACH – COMPASS - Eligible CAD with or without PAD N = 904	REACH – COMPASS - Eligible PAD with or without CAD N = 509
CV death, MI or stroke	13.4% [11.3 - 15.8]	11.6% [9.1 - 14.8]	13.2% [9.2 - 18.8]	19.1% [13.9 - 26.1]	13.4% [11.1 - 16.3]	15.7% [12.4 - 19.9]
All-cause mortality	11.2% [9.3 - 13.4]	9.0% [6.8 - 11.7]	11.2% [7.7 - 16.1]	17.9% [12.7 - 24.8]	11.1% [9.0 - 13.7]	14.1% [10.9 – 18.0]
CV death	7.0% [5.5 - 8.9]	5.8% [4.1 - 8.1]	6.3% [3.8 - 10.3]	11.7% [7.5 - 18.1]	7.2% [5.5 - 9.5]	8.6% [6.2 – 12.0]
Non CV death	4.5% [3.3 - 6.1]	3.4% [2.1 - 5.4]	5.2% [2.9 - 9.4]	6.9% [3.9 - 12.3]	4.2% [2.9 - 6.0]	5.9% [3.9 – 9.0]
Non-fatal MI	4.1% [2.9 - 5.7]	3.0% [1.8 - 4.8]	5.7% [3.0 - 10.9]	5.3% [3.0 - 9.4]	3.5% [2.4 - 5.1]	5.6% [3.6 - 8.8]
Non-fatal Stroke	3.5% [2.4 - 5.1]	3.6% [2.2 - 5.9]	3.1% [1.4 - 6.7]	3.8% [1.7 - 8.4]	3.6% [2.4 - 5.5]	3.4% [1.9 - 5.8]
Serious bleeding, % [CI 95]	2.5% [1.6 – 3.4]	2.3% [1.2 – 3.5]	2.4% [0.6 – 4.2]	3.2% [0.9 – 5.5]	2.5% [1.5 – 3.6]	2.7% [1.3 – 4.2]

CAD: coronary Artery Disease, CI: Confidence Interval, CV: Cardiovascular, MI: Myocardial Infarction, PAD: Peripheral Artery Disease,

Table 3: Occurrences of treatment patterns changes during follow-up for the overall “REACH – COMPASS – Eligible” population, and according to CAD ± PAD status.

	REACH COMPASS Eligible Total N = 1,194		CAD only (without PAD) N = 685		PAD only (without CAD) N = 290		CAD and PAD N = 219		CAD (with or without PAD) N = 904		PAD (with or without CAD) N = 509	
	1-year FU	4-year FU	1-year FU	4-year FU	1-year FU	4-year FU	1-year FU	4-year FU	1-year FU	4-year FU	1-year FU	4-year FU
Antiplatelet agents, n (%)	1041 (90.1%)	689 (87.7%)	599 (90.3%)	397 (86.7%)	248 (87.9%)	167 (86.1%)	194 (92.4%)	125 (93.3%)	793 (90.8%)	522 (88.2%)	442 (89.8%)	292 (89%)
Aspirin, n(%)	727 (63.3%)	486 (61.9%)	477 (72.3%)	320 (69.9%)	129 (46.2%)	87 (45.1%)	121 (57.6%)	79 (59%)	598 (68.7%)	399 (67.4%)	250 (51.1%)	166 (50.8%)
Oral anticoagulant treatments, n (%)	33 (2.9%)	52 (6.6%)	21 (3.2%)	37 (8.1%)	7 (2.5%)	9 (4.6%)	5 (2.4%)	6 (4.5%)	26 (3%)	43 (7.3%)	12 (2.5%)	15 (4.6%)
Beta-blockers, n (%)	589 (51.2%)	421 (53.9%)	406 (61.5%)	283 (62.1%)	66 (23.6%)	57 (29.5%)	117 (55.5%)	81 (61.4%)	523 (60.1%)	364 (61.9%)	138 (42.5%)	138 (42.5%)
Lipid lowering drugs, n (%)	978 (84.8%)	683 (87%)	571 (86.5%)	398 (86.9%)	220 (77.7%)	162 (83.9%)	187 (89%)	123 (91.8%)	758 (87.1%)	521 (88%)	407 (82.6%)	285 (87.2%)
ACE inhibitors or ARB, n (%)	722 (62.6%)	542 (69.1%)	412 (62.3%)	316 (69.1%)	175 (62.1%)	135 (69.6%)	135 (64%)	91 (68.4%)	547 (62.7%)	407 (69%)	310 (62.9%)	226 (69.1%)
Antidiabetic agents, n (%)	382 (33.2%)	267 (34.1%)	227 (34.3%)	150 (32.9%)	86 (30.5%)	60 (31.1%)	69 (33.2%)	57 (42.5%)	296 (34%)	207 (35.1%)	155 (31.6%)	117 (35.8%)

ACE: Angiotensin Converting Enzyme, ARB: Angiotension Receptor Blocker, CAD: coronary Artery Disease, FU: Follow-Up, PAD: Peripheral Artery Disease,