Assessment of patients with coronary artery disease who may benefit from the use of rivaroxaban in the real world: implementation of the COMPASS trial in the TERCET registry population

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Title
Assessment of patients with coronary artery disease who may benefit from the use of rivaroxaban in the real world: implementation of the COMPASS trial in the TERCET registry population.

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Short title
Implementation of the COMPASS trial in the TERCET registry population

The name of the trial registry
The Hyperlipidemia Therapy in tERtiary Cardiological cEnTer Zabrze (TERCET) Registry

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Abstract

Introduction: Positive outcomes of the COMPASS trial raise questions about the proportion of patients who could benefit from additional therapy with rivaroxaban in real-world practice.

Objectives: To describe the proportion of patients from the TERCET registry with significant coronary artery disease (TERCET-CAD) who could benefit from the use of rivaroxaban and to assess the clinical characteristics and long-term prognosis in comparison to the corresponding measures in the COMPASS trial.

Patients and methods: The COMPASS criteria were applied in the TERCET-CAD population. Patients from the TERCET-CAD population who met the criteria of the COMPASS trial were included in the COMPASS-like group. The baseline characteristics and long-term outcomes of the COMPASS-like group from the TERCET-CAD population were compared with the corresponding measures in the acetylsalicylic acid (ASA)-alone arm from the COMPASS trial.

Results: Among 12,286 patients in the TERCET-CAD population, the COMPASS-like group comprised 3,884 patients (31.6%). COMPASS-like patients were characterized by older age and more frequent occurrence of CAD risk factors than those in the ASA-alone arm of the COMPASS trial. The rate of composite endpoint in the COMPASS-like group was 9%, and in the ASA-alone arm of the COMPASS trial, it was 6%.

Conclusions: One-third of the TERCET-CAD population met the COMPASS criteria and could potentially benefit from low-dose rivaroxaban therapy. Unfavorable clinical profiles and higher rates of adverse events in the TERCET registry compared to those in the
COMPASS trial may predict greater benefits from the implementation of low-dose rivaroxaban in the real-world population.

**Key words**

COMPASS trial; coronary artery disease; external applicability; TERCET registry

**Main text**

**INTRODUCTION**

Despite the introduction of novel pharmacotherapy and the widespread use of revascularization, stable coronary artery disease (CAD) is still the most common cause of mortality and morbidity in the general population [1-3]. Patients with a diagnosis of stable CAD are at risk for adverse ischemic events and, as a consequence, cardiovascular death [4-6]. Given the activation of platelets and the coagulation cascade in atherosclerosis [7], one of the directions of contemporary research in stable CAD is the evaluation of adding various antithrombotic therapies to acetylsalicylic acid (ASA) in tertiary prevention [8,9]. Previous randomized controlled trials (RCTs) did not confirm that additional use of clopidogrel [10], ticagrelor [11], vorapaxar [12] or vitamin K [13] antagonists in patients with stable CAD was associated with measurable benefits in comparison to antithrombotic therapy limited to ASA. Recently, published results of an international, multicenter randomized Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS; ClinicalTrials.gov number: NCT01776424) trial indicated that adding low-dose rivaroxaban (2.5 mg twice daily) to ASA improves long-term outcomes in a selected population of patients with stable CAD [14-16].

As with any RCT [17-19], strict inclusion and exclusion criteria may cause difficulties in implementing the results from the COMPASS trial in the full spectrum of a stable CAD
population [14]. Patients enrolled in RCTs often have a lower cardiovascular risk than a real-world population [20-22], which may also change the benefits and risks of applying novel technologies or drugs [17,19]. Therefore, positive outcomes of the COMPASS trial raise questions about the proportion of patients in routine clinical practice who could benefit from additional therapy with low-dose rivaroxaban. Current guidelines of the European Society of Cardiology (ESC) emphasize the necessity of obtaining evidence from unselected patients and validated registries in order to refer the results of RCTs to real-world practice [23-25].

Data from the Hyperlipidemia Therapy in the tERtiary Cardiological cEnTer (TERCET) registry [26] encompassing a population with CAD allows an analysis of the proportion of patients who could benefit from the use of rivaroxaban as well as an assessment of clinical characteristics and long-term prognosis in comparison to those in the COMPASS trial.

PATIENTS AND METHODS

COMPASS trial

The design [14] and outcomes [15] of the COMPASS trial have been described previously. In brief, the COMPASS trial was a double-blind, placebo-controlled, randomized trial of 27,395 patients with stable CAD or peripheral vascular disease. The study population was randomly assigned into three arms of antithrombotic strategies, as follows: rivaroxaban (2.5 mg twice daily) plus ASA, rivaroxaban-alone (5 mg twice daily) or ASA-alone. Of the total number of patients enrolled in the COMPASS trial, 24,824 (91%) had stable CAD [16]. During the 23-month mean follow-up, the combination of rivaroxaban (2.5 mg twice daily) with ASA was associated with a significant 26% reduction of the primary endpoint in comparison to that in the control arms. Moreover, the combination of rivaroxaban plus ASA
resulted in more major bleeding than that in the ASA-alone arm, but without a significant increase in the rates of intracranial or life-threatening bleeding.

TERCET registry

The design of the TERCET registry (ClinicalTrials.gov Identifier: NCT03065543) has been previously published [26]. Briefly, the TERCET registry is a prospective, observational study recruiting consecutive patients with ischemic heart disease (stable angina and acute coronary syndromes) hospitalized in a tertiary cardiology center with an on-site cardiac surgery facility.

The primary outcome measure of the TERCET registry is the evaluation of the impact of treatment on the lipid profile and long-term prognosis of patients with ischemic heart disease. The diagnosis of CAD based on clinical manifestation, coronary angiography, and additional test results was in accordance with contemporary ESC guidelines [23-25]. Patients with vasospastic or microvascular angina were also included in the registry. Diagnostic and therapeutic strategies, including pharmacological and interventional treatment, were used in accordance with the current recommendations of the ESC [23-25]. Each patient enrolled in the TERCET registry underwent coronary angiography. The data on long-term follow-up, including cause of death and exact date of death and cardiovascular events, were obtained from the official registry of the National Health Fund, guaranteeing complete data collection. According to the ICD-10, myocardial infarction was defined as I21-22 codes, whereas stroke was defined as I60-64 codes. Follow-up was available for all patients. The TERCET registry has been granted approval by the Institutional Review Board, and it is in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.
TERCET-CAD population

For the purposes of the present study, of all patients in the TERCET registry hospitalized between 2006 and 2016, only stable patients (with stable angina or one year after an acute coronary syndrome) with significant CAD were included. Significant CAD was defined as prior myocardial infarction (MI), history of percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), ≥ 50% stenosis of the left main (LM) branch or proximal segment of the left anterior descending (LAD) branch of the left coronary artery, or ≥ 70% stenosis in other segments of the coronary arteries.

Patients with lacking data on parameters listed in the COMPASS criteria (n=1,887) were not included in the present analysis (Supplementary Material 1). The remaining patients comprised the TERCET-CAD population.

COMPASS criteria in the TERCET-CAD population

First, we applied the COMPASS inclusion criteria [14] to the TERCET-CAD population (Figure 1):

1. CAD according to the COMPASS criteria was defined as the occurrence of one of the following:
   - MI within the last 20 years, or
   - Multivessel coronary disease with symptoms or with a history of stable or unstable angina, or
   - Multivessel PCI, or
   - Multivessel CABG surgery

2. Patients who met the above criteria also met at least one of the following criteria:
   - Age ≥65 years, or
• Age <65 years and documented atherosclerosis or revascularization involving at least two vascular beds (the aorta, arterial supply to the brain, gastrointestinal tract, lower limbs, upper limbs, kidneys) or at least two additional risk factors (current smoking, diabetes mellitus, renal dysfunction with estimated glomerular filtration rate <60 ml/min, heart failure, ischemic stroke ≥1 month prior to inclusion)

The TERCET-CAD patients who did not meet the above inclusion criteria of the COMPASS trial were assigned to the COMPASS-not-included group.

Subsequently, among the remaining TERCET-CAD population, the following exclusion criteria of the COMPASS trial [14] were applied:

1. High risk of bleeding
2. Stroke within 1 month or any history of hemorrhagic or lacunar stroke
3. Severe heart failure with known ejection fraction <30% or New York Heart Association (NYHA) class III or IV symptoms
4. Estimated glomerular filtration rate <15 mL/min
5. The need for dual antiplatelet therapy, other non-ASA antiplatelet therapy, or oral anticoagulant therapy
6. Known noncardiovascular disease that is associated with poor prognosis (e.g., metastatic cancer)
7. History of hypersensitivity or known contraindication for rivaroxaban, ASA, or excipients, if applicable
8. Other exclusion criteria of the COMPASS trial

The remaining TERCET-CAD patients who met at least one of the above exclusion criteria of the COMPASS trial were assigned to the COMPASS-excluded group.
Patients from the TERCET-CAD population who met the inclusion criteria and did not meet the exclusion criteria of the COMPASS trial were the target study group, namely, the COMPASS-like group.

The data available in the TERCET registry allow defining all the inclusion and exclusion criteria of the COMPASS trial with a few exceptions. First, the definition of chronic heart failure in the TERCET registry has been defined as the presence of left ventricular dysfunction with left ventricle ejection fraction ≤ 35% or previous implantation of a device with a cardioverter-defibrillator function as part of the primary prevention of sudden cardiac death (except for patients with documented diagnosis of hypertrophic cardiomyopathy). In the COMPASS trial, chronic heart failure was determined based on clinical diagnosis in the patient's medical history [14-15]. Additionally, in the TERCET registry, the high risk of bleeding was based on the HAS-BLED score (high risk of bleeding ≥ 3 points) [27]. In the COMPASS trial, assessing the high risk of bleeding was left to investigator discretion. The exclusion criterion for hypersensitivity or known contraindications to the use of drugs is limited to either rivaroxaban or ASA, without taking into account pantoprazole (whose administration in the COMPASS trial was also assessed) [14].

Primary outcome measure

The primary endpoint in the COMPASS trial was a composite of cardiovascular death, stroke, or MI [14]. The study was stopped because of superiority of the rivaroxaban-plus-ASA group after a mean follow-up of 23 months [15-16]. Respectively, in the TERCET registry, due to the lack of information about the cause of death, all-cause death in the composite endpoint at the 24-month follow-up was used.
Statistical analysis

The baseline characteristics and long-term outcomes of the COMPASS-like group from the TERCET-CAD population were compared with the ASA-alone arm from the COMPASS-CAD substudy by Student’s t-test for continuous parameters and Chi-square tests for categorical parameters. Continuous variables are summarized using the arithmetic mean with standard deviation (SD) or median with quartiles 1 and 3 (Q1-Q3). A two-sided p-value of <0.05 was considered significant. The STATISTICA 10 software (StatSoft, Inc., Tulsa, Oklahoma) was used for all calculations.

RESULTS

Identification of the COMPASS-like group

A flow chart for the identification of patients meeting the COMPASS criteria in the TERCET-CAD population (the COMPASS-like group) is depicted in Figure 1. Among 12,286 patients of the TERCET-CAD population, the inclusion criteria of the COMPASS trial in 7,109 patients (57.9% of the entire population) were met. The remaining 5,177 patients (42.1% of the entire population) did not meet the COMPASS inclusion criteria (the COMPASS-not-included group).

Out of 7,109 people who met the inclusion criteria, in the next step, the exclusion criteria for the COMPASS study were used. Based on these criteria, 3,225 patients (26.2% of the entire population) excluded from further analysis were assigned to the COMPASS-excluded group. After implementation of the inclusion and exclusion criteria, the remaining 3,884 patients (31.6% of the entire population) was a study group that would potentially meet the COMPASS criteria in the TERCET-CAD population (the COMPASS-like group).

The percentage of the study groups in the TERCET-CAD population according to the COMPASS criteria is presented in Figure 2.
COMPASS criteria in the TERCET-CAD population

The main criteria for not meeting the inclusion criteria or meeting the exclusion criteria used in the TERCET-CAD population are presented in Figure 3. The main reasons for not meeting the inclusion criteria were as follows:

1. In 33.4% of cases, failure to meet the CAD definition according to the COMPASS criteria (n=1,729).
2. In 66.6% of cases, failure to meet the age criterion and the occurrence of risk factors (n=3,448).

In the COMPASS-excluded group, the main reasons for exclusion were as follows (with the possibility of several criteria for one patient):

1. Severe heart failure with known ejection fraction <30% or NYHA class III or IV symptoms (in 40.5% of patients)
2. High risk of bleeding defined as a HAS-BLED score ≥ 3 points (in 37.4% of patients)
3. Need for oral anticoagulant therapy (in 32.2% of patients)
4. Need for dual antiplatelet therapy or other non-ASA antiplatelet therapy (in 12.4% of patients)
5. Estimated glomerular filtration rate < 15 mL/min/1.73 m² (in 0.8% of patients)

COMPASS-like group in the TERCET-CAD population vs the ASA-alone arm of the COMPASS trial

A comparison of the COMPASS-like group (meeting the COMPASS criteria in the TERCET-CAD population) with the ASA-alone arm of the COMPASS trial is presented in Tables 1 and 2. The COMPASS-like patients were older. Male sex, diabetes mellitus, arterial
hypertension, and prior PCI were also more prevalent in the COMPASS-like patients. On the other hand, peripheral vascular disease and chronic heart failure were less prevalent.

Regarding medical therapy, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, statins and beta-blockers were used more frequently in the COMPASS-like group in comparison to the ASA-alone arm of the COMPASS trial.

In the TERCET-CAD registry, the follow-up was 24 months and was completed for all patients, whereas in the COMPASS trial, the mean follow-up was 23 months. The rate of composite endpoint in the COMPASS-like group was 9% (all-cause death, MI, or stroke) and in the ASA-alone arm of the COMPASS trial was 6% (cardiovascular death, MI, or stroke; \( P < 0.0001 \)). In addition, in the COMPASS-like group, all-cause death (6% vs 4%; \( P < 0.0001 \)) and incidence of MI (3% vs 2%; \( P = 0.006 \)) were significantly more frequent than in the ASA-alone arm of the COMPASS trial. There were no differences in other adverse cardiovascular events, such as stroke (2% vs 2%; \( P = 0.93 \)) or revascularization (7% vs 7%; \( P = 0.92 \)), between the analyzed groups.

Not-included vs included vs excluded groups of the TERCET-CAD population

The baseline characteristics and long-term outcomes of the COMPASS-like, the COMPASS-not-included and the COMPASS-excluded groups are shown in Table 3. In general, the COMPASS-not-included group was characterized by a lower incidence of CAD risk factors, comorbidities and the most favorable long-term prognosis. Conversely, patients in the COMPASS-excluded group had the highest rate of risk factors and worse long-term outcomes.
DISCUSSION

The results of the large-scale, prospective TERCET registry of a real-world population with CAD showed that 31.6% of patients met the COMPASS criteria. The remaining patients were ineligible for further analysis due to noncompliance with the inclusion criteria (42.1%) or fulfillment of the exclusion criteria (26.2%) of the COMPASS trial.

The possibility of external applicability of the COMPASS criteria in two large-scale international registries was analyzed [28-29]. The first of them was the Reduction of Atherothrombosis for Continued Health (REACH) registry encompassing patients over 45 years of age with a diagnosed atherosclerosis (CAD, peripheral or cerebral artery disease) or at least three risk factors for atherosclerosis [28]. The COMPASS criteria were met in 53% of the analyzed population of the REACH registry. The different rate of eligibility based on the COMPASS criteria in the REACH registry compared to that in the present study may be due to differences in the applied methodology. First, in the REACH registry, due to the lack of accurate information regarding the number of treated vessels and the degree of atherosclerosis progression in the coronary arteries, a less rigorous definition of CAD was adopted. In addition, the REACH registry did not have data on seven exclusion criteria from the COMPASS trial, including severe heart failure (left ventricular ejection fraction <30%, NYHA functional class III or IV), history of cancer, or hypersensitivity to rivaroxaban and ASA. Moreover, because of a lack of detailed recommendations in the COMPASS trial protocol on the definition of high risk of bleeding [14], the REACH bleeding risk score was used [30]. As the authors admit, the mentioned limitations could lead to the overestimation of a group that meets the COMPASS criteria in the REACH registry.

The second study evaluating the external applicability of the COMPASS criteria in the real-world population analyzed the FAST-MI 2005, 2010, and 2015 registries, involving patients diagnosed with a recent MI [29]. For the purpose of adapting the methodology of the
COMPASS trial, the FAST-MI population was included for analysis one year (entry point) after the occurrence of MI. The COMPASS criteria applied in the FAST-MI registries were met in 44% of the analyzed population. Notably, all patients had a previous MI, and as a consequence, they fulfilled the CAD definition according to the COMPASS trial [14]. The above-mentioned fact and not taking into account stable CAD patients in FAST-MI registries may also have caused an overestimation of the “true” eligibility of the COMPASS criteria in the real-world population. In contrast to the REACH and FAST-MI registries, in the present study, we were able to precisely define the inclusion and exclusion criteria in an unselected population of patients with stable CAD confirmed by coronary angiography. Furthermore, due to the implementation of a widely used HAS-BLED score, a high risk of bleeding was standardized [27].

Despite a high level of evidence, outcomes from RCTs in routine clinical practice have been implemented with appropriate caution [17-19]. Patients strictly recruited for RCTs are usually characterized by lower cardiovascular risk than the real-world population [20-22]. The current study confirms this fact despite the use of comparable inclusion and exclusion criteria. The COMPASS-like group in the TERCET-CAD population was characterized by older age, more frequent occurrence of CAD risk factors and a less favorable long-term prognosis. Similar results were observed in the REACH and the FAST-MI registries [28-29]. Differences in the baseline characteristics and the long-term outcomes between the real-world population and participants of the COMPASS trial may suggest that the addition of rivaroxaban to tertiary prevention in routine clinical practice will be associated with even better treatment effects.

After discharge, the patients meeting the COMPASS criteria in the TERCET-CAD population were characterized by a higher rate of a composite endpoint than that in the ASA-alone arm of the COMPASS trial [16]. First of all, we had no information on causes of death
in our study. Therefore, the definition of all-cause mortality was applied, in contrast to the COMPASS trial, where cardiovascular mortality was included in the composite endpoint. Also, the long-term outcomes, in the context of a worse clinical profile of the TERCET-CAD population, should be considered. Potentially, the differences may also result from the fact that the participants of the COMPASS trial were closely followed up after discharge from the hospital [14]. This issue could be related to better compliance with medical recommendations and the appropriate reaction of the treating physician to the onset of new symptoms.

In RCTs, the clinical profile and outcomes of patients not included and excluded from the trial are usually not presented [17-19]. In addition to the evaluation of eligibility in the real-world population, the results of observational studies can often result in the generation of new research hypotheses. Therefore, future research should focus on populations not included in clinical trials. Referring to the above considerations to the present study, it could be expected that the COMPASS-not-included group had the most favorable—and the COMPASS-excluded group had the worst—clinical profile and long-term outcomes. It is also worth noting that, despite the more favorable characteristics of the COMPASS-not-included group, long-term outcomes were similar to those in the ASA-alone arm of the COMPASS trial [16]. Considering the relatively rigorous CAD definition adopted in the COMPASS trial [14], it seems reasonable to conduct RCTs evaluating the benefits of using additional rivaroxaban therapy in a population with any significant CAD.

Study strengths and limitations

The TERCET is a large-scale, prospective registry of unselected patients with CAD confirmed in coronary angiography and with an available follow-up obtained from the National Health Fund (the only payer in Poland). In addition to the typical advantages and limitations associated with the registry-based nature of the study, a few remarks should be
mentioned. The adopted definition of chronic heart failure is more detailed and the bleeding risk is higher in the TERCET registry than in the COMPASS trial [14], and other studies allow a more accurate estimation of cardiovascular risk in the study population. The recruitment of the COMPASS trial was conducted from February 2013 to May 2016, while the TERCET registry includes patients hospitalized between January 2006 and December 2016. Time differences in the enrolment period for both studies and, in consequence, the implementation of previous ESC recommendations may have translated into differences in the distribution of risk factors, management, tertiary prevention, and outcomes [31]. Therefore, the results of the present study should be interpreted with caution.

Conclusions

In summary, less than one-third of the population of the TERCET registry with significant CAD met the COMPASS criteria and could potentially benefit from low-dose rivaroxaban therapy. Unfavorable clinical profiles and the higher rate of adverse events in the TERCET registry compared to those in the COMPASS trial may result in greater benefits of implementation of low-dose rivaroxaban in the real-world population. Therefore, there is a need for further clinical trials in the routine clinical practice of the CAD population.

Contribution statement

Research idea and study design: PD, BH, MG; data acquisition: PD, BH; data analysis/interpretation: PD, BH, MG; statistical analysis: PD; supervision or mentorship: MG. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.
References


18. Rothwell PM. External validity of randomised controlled trials: “to whom do the results of this trial apply?” Lancet. 2005; 365: 82-93.


Figure legends

Figure 1. Flow chart for identification of the COMPASS-like group in the TERCET-CAD population based on the COMPASS trial inclusion and exclusion criteria.

^aSignificant CAD was defined as hemodynamically significant stenosis in one or more coronary arteries (≥50% diameter stenosis in the LM coronary artery or proximal segment of the left anterior descending artery, or ≥70% stenosis diameter in other segments).

^bBecause CAD involves disease in the coronary vasculature, only one additional vascular bed is required.

^cRisk factors: current smoking, diabetes mellitus, renal dysfunction with estimated glomerular filtration rate <60 ml/min, heart failure, nonlacunar ischemic stroke ≥1 month ago.

Abbreviations: APT, antiplatelet therapy; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; OAC, oral anticoagulants; PCI, percutaneous coronary intervention; SA, stable angina; UA, unstable angina.
**TERCET-CAD population**

TERCET-CAD population, defined as:
- Prior MI, or
- Prior PCI, or
- Prior CABG, or
- Significant CAD

N = 12,286

**COMPASS inclusion criteria**

COMPASS-CAD, defined as:
- MI within the last 20 years, or
- Multi-vessel CAD with symptoms or with history of SA or UA, or
- Multi-vessel PCI, or
- Multi-vessel CABG surgery

Subjects with COMPASS-CAD must also meet at least one of the following criteria:
- Age ≥ 65, or
- Age < 65 and documented atherosclerosis or revascularization involving at least 2 vascular beds or at least 2 additional risk factors.

**COMPASS-not-included group**

TERCET-CAD population not fulfilling the inclusion criteria of COMPASS
n = 5,177 (42.1%)

**TERCET-CAD population fulfilling the inclusion criteria of COMPASS**

n = 7,109 (57.9%)

**COMPASS exclusion criteria**

- High risk of bleeding
- Stroke within 1 month or any history of hemorrhagic or lacunar stroke
- Severe heart failure with known LVEF <30% or NYHA class III or IV
- eGFR<15 mL/min
- Need for DAPT, other non-aspirin APT, or OAC
- Known non-cardiovascular disease that is associated with poor prognosis e.g., metastatic cancer or that increases the risk of an adverse reaction to study interventions.
- History of hypersensitivity or known contraindication to nivaroxybar, aspirin.

**COMPASS-excluded group**

TERCET-CAD population fulfilling the exclusion criteria of COMPASS
n = 3,225 (26.2%)

**COMPASS-like group**

TERCET-CAD population fulfilling the inclusion and not fulfilling the exclusion criteria of COMPASS
n = 3,884 (31.6%)
Figure 2. The proportion of the COMPASS-like, the COMPASS-not-included (not fulfilling the inclusion criteria of the COMPASS trial), and the COMPASS-excluded (fulfilling the exclusion criteria of the COMPASS trial) groups of the TERCET-CAD population.

**TERCET-CAD population**

N = 12286

- **31.6%** COMPASS-like  
  n = 3,884

- **26.2%** COMPASS-excluded  
  n = 3,225

- **42.1%** COMPASS not-included  
  n = 5,177
Figure 3. Main reasons for the COMPASS inclusion and exclusion criteria in the TERCET-CAD population.

**COMPASS-not-included**
TERCET-CAD population not fulfilling the inclusion criteria of COMPASS

n = 5,177 (42.1%)

**COMPASS-excluded**
TERCET-CAD population fulfilling the exclusion criteria of COMPASS

n = 3,225 (26.2%)

Abbreviations: CAD, coronary artery disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OAC, oral anticoagulants.
### Tables

Table 1. Baseline characteristics of the COMPASS-like group (from the TERCET-CAD population) and the COMPASS-CAD ASA-alone arm.

<table>
<thead>
<tr>
<th>Variable</th>
<th>COMPASS-like (from TERCET-CAD) n = 3,884</th>
<th>COMPASS-CAD ASA-alone arm n = 8,261</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; median (Q1-Q3)</td>
<td>70 (65-75)</td>
<td>69 (65-73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1,252 (32)</td>
<td>1,646 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>2,632 (68)</td>
<td>6,615 (80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body-mass index, kg/m²; mean (SD)</td>
<td>28.4 (4.4)</td>
<td>28.5 (4.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²; mean (SD)</td>
<td>79.7 (23.8)</td>
<td>73.7 (17.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg; mean (SD)</td>
<td>133 (18)</td>
<td>135 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg; mean (SD)</td>
<td>78 (11)</td>
<td>78 (10)</td>
<td>0.92</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>956 (25)</td>
<td>1,687 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>1,762 (45)</td>
<td>3,908 (47)</td>
<td>0.046</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1,629 (42)</td>
<td>3,040 (37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>3,057 (79)</td>
<td>6,218 (75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral artery disease, n (%)</td>
<td>654 (17)</td>
<td>1,641 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>2,673 (69)</td>
<td>5,721 (69)</td>
<td>0.64</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>3,168 (82)</td>
<td>4,905 (59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>1,231 (32)</td>
<td>2,586 (31)</td>
<td>0.67</td>
</tr>
<tr>
<td>Multivessel CAD, n (%)</td>
<td>2,423 (62)</td>
<td>5,043 (61)</td>
<td>0.16</td>
</tr>
<tr>
<td>Chronic heart failure\a, n (%)</td>
<td>437 (11)</td>
<td>1,912 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>109 (3)</td>
<td>268 (3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB, n (%)</td>
<td>3,452 (89)</td>
<td>5,939 (72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-lowering drug, n (%)</td>
<td>3,548 (93)</td>
<td>7,573 (92)</td>
<td>0.045</td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>3,641 (94)</td>
<td>6,154 (75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eastern European, n (%)</td>
<td>3,884 (100)</td>
<td>1,487 (18)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\aFor the COMPASS-like group, chronic heart failure was defined as left ventricular ejection fraction ≤ 35% or history of implantation of a cardioverter-defibrillator for primary prevention of sudden cardiac death (excluding hypertrophic cardiomyopathy).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate.
Table 2. Major efficacy outcomes of the COMPASS-like group (from the TERCET-CAD population) and the COMPASS-CAD ASA-alone arm.

<table>
<thead>
<tr>
<th>Variable</th>
<th>COMPASS-like (from TERCET-CAD) n = 3,884</th>
<th>COMPASS-CAD ASA-alone arm n = 8,261</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, stroke, or cardiovascular death&lt;sup&gt;a&lt;/sup&gt;, n (%)</td>
<td>360 (9)</td>
<td>460 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>217 (6)</td>
<td>339 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>125 (3)</td>
<td>195 (2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>62 (2)</td>
<td>130 (2)</td>
<td>0.93</td>
</tr>
<tr>
<td>Coronary revascularization, n (%)</td>
<td>262 (7)</td>
<td>553 (7)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

<sup>a</sup>For the COMPASS-like group, due to the lack of information about the cause of death, “all-cause” was used.
Table 3. Baseline characteristics and major efficacy outcomes of the COMPASS-like, the COMPASS-not-included (not fulfilling the inclusion criteria of the COMPASS trial) and the COMPASS-excluded (fulfilling the exclusion criteria of the COMPASS trial) groups of the TERCET-CAD population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>COMPASS-not-included n = 5,177 (42.1%)</th>
<th>COMPASS-like n = 3,884 (31.6%)</th>
<th>COMPASS-excluded n = 3,225 (26.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; median (Q1-Q3)</td>
<td>59 (55-64)</td>
<td>70 (65-75)</td>
<td>72 (67-77)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1,407 (27)</td>
<td>1,252 (32)</td>
<td>1,070 (33)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>5,177 (73)</td>
<td>2,632 (68)</td>
<td>2,155 (67)</td>
</tr>
<tr>
<td>Body-mass index, kg/m^2; mean (SD)</td>
<td>28.7 (4.5)</td>
<td>28.4 (4.4)</td>
<td>28.7 (4.7)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m^2; mean (SD)</td>
<td>91.3 (23.6)</td>
<td>79.7 (23.8)</td>
<td>71.2 (24.7)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg; mean (SD)</td>
<td>136 (22)</td>
<td>133 (18)</td>
<td>141 (28)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg; mean (SD)</td>
<td>81 (13)</td>
<td>78 (11)</td>
<td>81 (14)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>1,278 (25)</td>
<td>956 (25)</td>
<td>526 (16)</td>
</tr>
<tr>
<td>Former smoker, n (%)</td>
<td>2,541 (49)</td>
<td>1,762 (45)</td>
<td>1,382 (43)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1,236 (24)</td>
<td>1,629 (42)</td>
<td>1,526 (47)</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>3,772 (73)</td>
<td>3,057 (79)</td>
<td>2,691 (83)</td>
</tr>
<tr>
<td>Peripheral artery disease, n (%)</td>
<td>223 (4)</td>
<td>654 (17)</td>
<td>865 (27)</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>2,652 (51)</td>
<td>2,673 (69)</td>
<td>2,429 (75)</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>4,332 (84)</td>
<td>3,168 (82)</td>
<td>2,677 (83)</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>827 (16)</td>
<td>1,231 (32)</td>
<td>949 (29)</td>
</tr>
<tr>
<td>Multivessel CAD, n (%)</td>
<td>1,627 (32)</td>
<td>2,423 (62)</td>
<td>1,941 (60)</td>
</tr>
<tr>
<td>Chronic heart failure, n (%)</td>
<td>378 (7)</td>
<td>437 (11)</td>
<td>1,169 (36)</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, % (SD)</td>
<td>48.6 (9.2)</td>
<td>46.9 (8.2)</td>
<td>39.6 (12.5)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>110 (2)</td>
<td>109 (3)</td>
<td>542 (17)</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB, n (%)</td>
<td>4,584 (89)</td>
<td>3,452 (89)</td>
<td>2,731 (85)</td>
</tr>
<tr>
<td>Lipid-lowering drug, n (%)</td>
<td>4,762 (93)</td>
<td>3,548 (93)</td>
<td>2,870 (91)</td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>4,800 (93)</td>
<td>3,641 (94)</td>
<td>3,021 (94)</td>
</tr>
<tr>
<td>MI, stroke, or cardiovascular death, n (%)</td>
<td>318 (6)</td>
<td>360 (9)</td>
<td>519 (16)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>189 (4)</td>
<td>217 (6)</td>
<td>373 (11)</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>113 (2)</td>
<td>125 (3)</td>
<td>130 (4)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>38 (1)</td>
<td>62 (2)</td>
<td>85 (3)</td>
</tr>
<tr>
<td>Coronary revascularization, n (%)</td>
<td>293 (6)</td>
<td>262 (7)</td>
<td>208 (6)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate.