COMPASS criteria applied to a contemporary cohort of unselected patients with stable coronary artery diseases: insights from the START registry

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Running title: COMPASS criteria in the START Registry

Word count: 3192 (text only); 2 Tables; 4 Figures

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ABSTRACT

Background. Recently, the COMPASS trial demonstrated that dual therapy reduced cardiovascular outcomes compared with aspirin alone in patients with stable atherosclerotic disease.

Methods and Results. We sought to assess the proportion of patients eligible for the COMPASS trial and to compare the epidemiology and outcome of these patients with those without COMPASS inclusion or with any exclusion criteria in a contemporary, nationwide cohort of patients with stable coronary artery disease (CAD).

Among the 4068 patients with detailed information allowing evaluation of eligibility, 1416 (34.8%) did not fulfill the inclusion criteria (COMPASS-Not-Included), 841 (20.7%) had exclusion criteria (COMPASS-Excluded) and the remaining 1811 (44.5%) were classified as COMPASS-Like. At 1 year, the incidence of major adverse cardiovascular event (MACE), a composite of cardiovascular death, myocardial infarction and stroke, was 0.9% in the COMPASS-Not-Included and 2.0% in the COMPASS-Like (p=0.01), and 5.0% in the COMPASS-Excluded group (p<0.0001 for all comparisons). Among the COMPASS-Like population, patients with multiple COMPASS enrichment criteria presented a significant increase in the risk of MACE (from 1.0% to 3.3% in those with 1 and ≥3 criteria, respectively; p=0.012), and a modest absolute increase in major bleeding risk (from 0.2% to 0.4%, respectively; p=0.46).

Conclusions. In a contemporary real-world cohort registry of stable CAD, most patients resulted as eligible for the COMPASS. These patients presented a considerable annual risk of MACE that consistently increases in the presence of multiple risk factors.

Key words: COMPASS trial; rivaroxaban; START registry; coronary artery disease.

INTRODUCTION

Recently, the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial demonstrated that a dual pathway approach, based on low dose rivaroxaban plus aspirin, reduced cardiovascular (CV) outcomes and improved net clinical benefits compared with aspirin alone, in patients with stable coronary artery diseases (CAD) or peripheral artery diseases (PAD) (1-3). Based on these data, it is reasonable to assume that, when this innovative and effective pharmacological strategy will be commonly available on the market, it might considerably change the management of patients with atherosclerotic vascular disease (4).

Patients included in clinical trials are usually highly selected and do not have the same risk level faced in daily practice (5,6). In this regard, treating with novel pharmacological strategies patients at dissimilar risks may produce different benefits or be associated with unidentified disadvantages. For these reasons, the translation of evidence from randomized clinical trials to contemporary clinical scenarios is a key issue, especially in current healthcare systems that are in charge of an increasing number of patients at elevated risk.

Using the data from the nationwide STable Coronary Artery Diseases RegisTry (START) study (7,8), we sought to assess the proportion of COMPASS eligible patients in a contemporary cohort of patients with stable CAD managed by cardiologists in daily clinical practice. In addition, we set out to compare the epidemiology and outcome of COMPASS eligible patients with those without inclusion or with any exclusion criteria of the COMPASS trial in a real-world setting.

METHODS

The design and main results of the START registry have been published previously (7). Briefly, the START was a prospective, observational, nationwide study endorsed by the Italian Association of Hospital Cardiologists (ANMCO) and aimed to evaluate the current presentation, management and treatment of patients with stable CAD as seen by cardiologists in clinical practice in Italy, during a 3-month period (7). Enrolment was made at the end of outpatient or day-hospital visit or at hospital discharge. Data on baseline characteristics, including demographics, risk factors and medical history, were collected. Information on the use of diagnostic cardiac procedures, type and timing of revascularization (if performed) and use of pharmacological or non-pharmacological therapies were recorded on an electronic case report form (CRF) at hospital discharge or the end of outpatient visit (7,8).

Optimal medical therapy (OMT) was defined as patients being prescribed aspirin or thienopyridine, b-blocker, and a statin, at the maximum tolerated dosage. To be categorized as receiving OMT, individual patients must have been either prescribed or had reported contraindications to all medications in each category (7). Data on the use of angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs) were recorded and could be used to calculate their use among those patients in whom they were clinically indicated. Therefore, given that the guidelines for stable CAD (9,10) recommend an ACE-I or ARB for some subgroups of patients, we also examined OMT, defined as patients being prescribed aspirin or thienopyridine, β-blockers, statins and ACE-Is or ARBs, if indicated by an ejection fraction of less than 40%, hypertension, diabetes or chronic renal dysfunction (eligible patients).

ANMCO invited to participate all Italian cardiology wards, including university teaching hospitals, general and regional hospitals, and private clinics receiving patients with stable CAD. No specific protocols or recommendations for evaluation, management, and/or treatment have been put forth during this observational study. However, guidelines for the management of patients with stable CAD have been discussed during the investigator

meetings (7).

All patients were informed of the nature and aims of the study and asked to sign an informed consent for the anonymous management of their individual data. Local Institutional Review Boards (IRB) approved the study protocol according to the current Italian rules.

One-hundred eighty-three cardiology centers included consecutive patients in the survey in different periods of 3 months between March 2016 and February 2017 (7).

Definitions of COMPASS populations

In order to estimate the COMPASS trial population in START registry, we excluded patients in whom detailed information regarding eligibility in COMPASS was incomplete or missing and patients enrolled in the START on the sole basis of having atherothrombotic risk factors alone without documented CAD and/or PAD, yielding a 'COMPASS-Evaluable' cohort, which is the study population for the present analysis. The main COMPASS inclusion and exclusion criteria (1) were applied to the 'COMPASS-Evaluable' population.

Patients meeting any COMPASS exclusion criteria (1), such as severe renal insufficiency (defined as an estimated glomerular filtration rate < 15 mL/min using the Cockroft-Gault formula), history of ischemic stroke in the past month and need for dual antiplatelet therapy (DAPT) or oral anticoagulant therapy (OAT) (1), were excluded (the 'COMPASS-Excluded' subset).

Then, patients were included in the 'COMPASS-Like' subset, if they had no exclusion criteria and fulfilled the COMPASS inclusion criteria (patients with CAD had to be aged >65 years; if aged <65 years they had to fulfill at least one additional 'enrichment' criterion such as documented atherosclerosis or prior revascularization involving at least two vascular beds or at least two additional risk factors among the following: current smoker, diabetes mellitus, estimated GFR < 60 mL/min, non-lacunar ischemic stroke >1 year, or heart failure) (1).

Patients with CAD < 65 years and no enrichment criteria or less than two additional risk factors were included in the 'COMPASS-Not-Included' subset.

Primary and secondary outcomes

The primary outcome of the present analysis was the occurrence of major adverse CV events (MACE), a composite of CV death, MI and stroke, (the same as for COMPASS trial (1)) in the 3 groups at 1-year follow-up. We also analyzed secondary outcomes such as all-cause death, any hospitalization and major bleeding at 1 year. Finally, we assessed the incidence of MACE and major bleeding events among the COMPASS-like population, according to the presence of single or multiple COMPASS enrichment criteria.

All patients were followed up by visits or telephone interviews by investigators at 1 year after enrolment. Interviews included questions related to the occurrence of events (cardiac, vascular, or others), planned and unplanned hospitalizations. Myocardial infarction (both ST-elevation or Non-ST-elevation MI) was defined according to the third universal definition of MI (11). Stroke was identified as an acute neurologic deficit lasting >24 hours and affecting the ability to perform daily activities with or without confirmation by imaging techniques. Major bleeding was classified according to the Thrombolysis In Myocardial Infarction (TIMI) criteria (12).

Statistical analysis

Categorical variables are presented as number and percentages and compared by the chi-square test. Continuous variables are presented as mean and standard deviation (SD), except for laboratory variables, which are reported as median and interquartile range (IQR). Continuous variables were compared by the analysis of variance (ANOVA), if normally distributed, or by the Kruskall-Wallis test, if not.

A multivariable analysis (logistic regression) was performed to estimate the risk of MACE (primary outcome) adjusting for the 3 study groups.

A p value < 0.05 was considered statistically significant. All tests were 2-sided. Analyses were performed with IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY.

RESULTS

From the 5070 consecutive patients with stable CAD enrolled in the START registry, 4068 were deemed as COMPASS-Evaluable (**Figure 1-panel A**); among these patients, 1416 (34.8%) were classified as COMPASS-Not-Included, 1811 (44.5%) as COMPASS-Like, and the remaining 841 (20.7%) as COMPASS-Excluded (**Figure 1-panel B**).

Baseline characteristics of patients in the three groups are shown in **Table 1**. As expected, patients in the COMPASS-Not-Included group were younger, presented a lower rate of CV and non-CV risk factors and a better hemodynamic profile compared with the other groups, while patients in the COMPASS-Excluded group presented the worst clinical and hemodynamic profile (**Table 1**). Accordingly, among the 3596 (88.4%) patients with coronary angiography data available, those deemed as COMPASS-Excluded presented a higher incidence of multivessel CAD compared to others (**Figure 2**).

At the time of discharge/end of the visit, patients in the COMPASS-Excluded group received more diuretics, mineralocorticoid receptor antagonist, nitrates and oral anticoagulant agents and less OMT (in both overall and eligible populations) compared to other groups (**Table 2**).

Events at Follow-up

At 1 year (median 369; IQR 362–378 days) from enrollment, the incidence of MACE was 0.9% in the COMPASS-Not-Included, 2.0% in the COMPASS-Like ($p=0.01$ for COMPASS-Not-Included vs COMPASS-Like) and 5.0% in the COMPASS-Excluded group ($p<0.0001$ for all comparisons) (**Figure 3).** The incidence of the single endpoints included in the composite primary outcome were as follows: 0, 0.4% and 3.3% for CV death, 0.8%, 0.8% and 1.1% for MI and 0.1%, 0.9% and 0.8% for stroke in COMPASS-Not-Included, COMPASS-Like and COMPASS-Excluded groups, respectively.

At logistic regression analysis, COMPASS-Excluded and COMPASS-Like features, compared to those of the COMPASS-Not-Included patients, were independently associated with MACE (odds ratio (OR) 12.9; 95% confidence intervals (CI): 7.8-21.4; $p<0.0001$ and OR 2.9; 95% CI: 1.7-4.8; $p<0.0001$, respectively).

The incidence of all secondary outcomes was significantly higher in the COMPASS-Excluded compared to COMPASS-Like, and higher in this latter compared to COMPASS-Non-Included group, with the exception of major bleedings that were comparable between COMPASS-Like and COMPASS-Excluded patients **(Figure 3).**

Among the COMPASS-Like population, patients with multiple enrichment criteria presented a significant increase in the risk of MACE (1.0%, 1.9% and 3.3% for those with 1, 2, and ≥3 criteria, respectively), and a modest absolute increase in the rate of major bleedings (0.2%, 0.5% and 0.4%, respectively) (**Figure 4**).

DISCUSSION

The major results of the present analysis including a large, nationwide, contemporary cohort of unselected stable CAD patients were the following: 1) patients who fulfill all criteria for enrollment in the COMPASS trial represent the majority of stable CAD patients; 2) COMPASS-Like patients present an absolute rate of MACE per year comparable to the aspirin arm of the COMPASS trial and steadily increasing with the presence of multiple COMPASS enrichment criteria 3) the presence of COMPASS exclusion criteria defines a population at highest risk of ischemic events.

The COMPASS was a randomized, double-blind trial comparing rivaroxaban given alone or in combination with aspirin as an alternative to aspirin monotherapy for the prevention of CV events in patients with stable CAD or PAD (1). Compared with aspirin alone, the combination of rivaroxaban 2.5 mg bid and aspirin reduced the risk of a composite of CV death, MI, or stroke through an average follow-up of about 2 years, at the cost of increased major bleeding, although a composite net clinical benefit endpoint incorporating risks of the most serious bleedings still favored the dual pathway approach (1). After the publication of the COMPASS trial, a few studies have assessed the external applicability of its results in unselected populations of patients with atherosclerotic diseases (13), at 1 year after MI (14) or undergoing coronary angiography (15). In these studies, the proportion of COMPASS-Like patients approximately ranged from a quarter to half of the analyzed populations (13-15). In the analysis of the Reduction of Atherothrombosis for Continued Health (REACH) registry (13), that included a large cohort of patients more similar to our population, such as those with established atherosclerotic disease, the incidence of COMPASS-Like patients was 53%, very closed to what we observed in the present analysis. Indeed, we included patients with stable CAD managed by specialists that is mostly the target population in which the combination strategy tested in the COMPASS trial should be used in clinical practice.

Our series is also more contemporary compared to others that refer to the first decade of 2000's (13-15). Notably, the START study (7) and the COMPASS trial (1) have been conducted in a matching

period of time, further increasing the reliability of the external applicability of the COMPASS trial results in our cohort. In this regard, the use of evidence-based medications and the rate of coronary revascularizations were comparable between the START and COMPASS participants, reflecting a population receiving a more contemporary management compared to other previously published observational studies, including the REACH analysis (13-15). Even the extent and severity of CAD, that was a criterion for inclusion in the COMPASS trial (not collected in the REACH registry CRFs (13)) was quite comparable between the COMPASS and the START, having approximately 60% of stable CAD patients enrolled in our registry with left main or multivessel CAD at coronary angiography. Accordingly, compared to the aspirin alone treatment arm of the overall (1) or CAD only (2) populations of the COMPASS trial, our group of COMPASS-Like patients experienced a similar rate of MACE (2.9% or 2.0% vs 2.0%/year, respectively). This similar incidence of ischemic events is of fundamental importance as it is expected to reliably translate into daily clinical practice the benefits of dual therapy noted in the COMPASS trial. Indeed, when low-dose rivaroxaban will become available for routine clinical use in Italy, we expect a further 20% relative risk reduction in MACE and mortality in stable CAD patients, as observed in the COMPASS (2). Notably, the annual rates of ischemic events observed in COMPASS trial and our series are nearly half as compared to those of patients deemed as COMPASS-Like in the REACH registry (4.2%/year) (13). This difference may further confirm the better management used in contemporary compared to earlier registries, but might also be related to different risk profiles, as suggested by the higher number of COMPASS-Like patients with multiple risk factors enrolled in REACH (13) compared to START registry (48% vs 26% with ≥3 COMPASS enrichment criteria). In this regard, Darmon et al. previously demonstrated in the COMPASS-Like population of the REACH registry, that patients with multiple COMPASS enrichment criteria had a dramatic increase in ischemic risk (16). This finding was confirmed even in our registry and has important implications for dual pathway prescription in clinical practice.

Our findings also confirmed the known observation that patients presenting with exclusion criteria

precluding eligibility in clinical trials represent a high-risk, usually undertreated subset with poor outcomes (5,6,17). Indeed, in our analysis the observed CV outcomes matched the severity predicted by baseline risk assessment in the three different subsets of the COMPASS Evaluable population (Not-Included, Like and Excluded), since the rate of ischemic CV events at 1 year was at least two-fold higher in each group compared to others.

Study Limitations

Our study must be evaluated in the light of some limitations. First, it suffers the same limitations as all observational non-interventional studies with differences with the standardized treatment regimen of a randomized trial. Therefore, comparisons and differences should be interpreted with caution. Second, although a small proportion of patients with PAD have been included in the present analysis, the START registry was focused on stable CAD and we did not collect detailed data on PAD, including the rate of asymptomatic carotid stenosis >70% that was an enrichment criterion of the COMPASS population. However, this latter condition was the less common (8.7%) among the COMPASS enrichment criteria and the only criterion not independently associated with a higher risk of MACE in previous real-world analyses (16). Third, the definition of major bleeding used in START was different from those employed in COMPASS (1) and precludes direct comparisons across studies. In addition, we have data of follow-up at 1 year only, while in other observational studies and in the COMPASS trial patients were followed for a longer period of time (11,13,1). However, at the landmark analysis of the COMPASS trial (1), the yearly rate of the primary ischemic endpoint did not change over time, therefore comparing the incidence of MACE per 100 patients/year seems reliable. Finally, the population of the START registry represents a nationwide sample in Italy, but cannot necessarily be extrapolated to other countries.

CONCLUSIONS

In a contemporary real-world cohort of patients with stable CAD, 45% of patients resulted as eligible, 35% non-eligible and 21% as excluded according to COMPASS criteria. In current clinical practice, the inclusion and enrichment criteria used in the COMPASS defined a population with a considerable annual risk of MACE that consistently increases in the presence of multiple risk factors, with a modest impact on the risk of major bleeding events.

Funding

The sponsor of both studies was the Heart Care Foundation, a non-profit independent organization, which also owns the database. Database management, quality control of the data and data analyses were under the responsibility of the ANMCO Research Centre Heart Care Foundation. The START study was partially supported by an unrestricted grant by Menarini, Italy. No compensations were provided to participating sites, investigators, nor members of the Steering Committee. The Steering Committee of both studies had full access to all of the data and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

L.D.L. has received honoraria for advisory boards or as speaker/chairman at scientific congresses from Amgen, Aspen, Astra-Zeneca, Bayer, Boehringer Ingelheim, Chiesi, Daiichi Sankyo, Eli Lilly, Menarini, Pfizer/BMS, Sanofi, Servier.

All other authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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FIGURE LEGEND

Figure 1. Flow chart for identification of COMPASS-Eligible population in the START registry (panel A) and proportion (%) of COMPASS-Like, COMPASS-Not-Included and COMPASS-Excluded patients within the COMPASS-Eligible population of the START registry (panel B).

CAD**:** coronary artery disease; PAD: peripheral artery disease

Figure 2. Extent of CAD (among the 3596 with data available) in the COMPASS-Not-Included, COMPASS-Like and COMPASS-Excluded groups.

Figure 3. Incidence of primary (CV death/MI/stroke) and secondary outcomes in the COMPASS-Not-Included, COMPASS-Like and COMPASS-Excluded groups.

CV**:** cardiovascular; MI: myocardial infarction

Figure 4. Association of multiple enrichment criteria with ischemic primary outcome (black bars) and bleeding (white bars) risks among the COMPASS-Like population.

Appendix

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tab

TABLE 1. Baseline clinical characteristics of the 3 groups.

	COMPASS NOT-INCLUDED N=1416	COMPASS LIKE N=1811	COMPASS EXCLUDED N=841	P values		
				Like vs Excluded	Excluded vs Not-Included	Like vs Not-Included
Age (years), mean ± SD	56.4 (6.5)	72.4 (7.6)	74.3 (7.3)	<0.0001	<0.0001	<0.0001
Age >75 years, n (%)	0	655 (36.2%)	403 (47.9%)	<0.0001	<0.0001	<0.0001
Females, n (%)	180 (12.7%)	398 (22.0%)	181 (21.5%)	0.792	<0.0001	<0.0001
BMI (kg/m^2), mean ± SD	27.7 (3.9)	27.2 (4.0)	27.2 (4.3)	0.793	0.009	<0.0001
Risk factors and comorbidities, n (%)						
Active smokers	338 (23.9%)	307 (17.0%)	98 (11.7%)	<0.0001	<0.0001	<0.0001
Hypercholesterolaemia	1043 (73.7%)	1361 (75.2%)	646 (76.8%)	0.353	0.095	0.334
Diabetes mellitus	240 (16.9%)	679 (37.5%)	321 (38.2%)	0.738	<0.0001	<0.0001
Hypertension	962 (67.9%)	1522 (84.0%)	706 (83.9%)	0.951	<0.0001	<0.0001
Chronic renal dysfunction*	22 (2.1%)	514 (34.8%)	378 (51.6%)	<0.0001	<0.0001	<0.0001
Peripheral artery disease	51 (3.6%)	229 (12.6%)	171 (20.3%)	<0.0001	<0.0001	<0.0001
COPD	74 (5.2%)	235 (13.0%)	177 (21.0%)	<0.0001	<0.0001	<0.0001
Malignancy	51 (3.6%)	0	218 (25.9%)	<0.0001	<0.0001	<0.0001
Depression	130 (9.2%)	174 (9.6%)	129 (15.3%)	<0.0001	<0.0001	0.680
Cardiovascular history, n (%)						
Previous stroke/TIA	19 (1.3%)	108 (6.0%)	97 (11.5%)	<0.0001	<0.0001	<0.0001
History of major bleeding	18 (1.3%)	0	62 (7.4%)	<0.0001	<0.0001	<0.0001
Atrial fibrillation	69 (4.9%)	0	475 (56.5%)	<0.0001	<0.0001	<0.0001
History of heart failure	34 (2.4%)	170 (9.4%)	358 (42.6%)	<0.0001	<0.0001	<0.0001
Prior MI	1161 (82.0%)	676 (80.4%)	1263 (89.2%)	0.318	<0.0001	<0.0001
Previous PCI	1050 (74.2%)	1229 (67.9%)	544 (64.7%)	0.106	<0.0001	<0.0001
Previous CABG	164 (11.6%)	351 (19.4%)	265 (31.5%)	<0.0001	<0.0001	<0.0001
Haemodynamic parameters, mean ± SD						
Ejection fraction, %	55.6 (8.0)	54.9 (8.1)	47.4 (13.6)	<0.0001	<0.0001	0.027
SBP, mmHg	126.9 (15.5)	132.5 (16.3)	128.1 (17.7)	<0.0001	0.072	<0.0001

DBP, mmHg	77.0 (9.2)	76.1 (9.0)	74.0 (9.7)	<0.0001	<0.0001	0.004
HR, bpm	65.4 (10.2)	65.5 (10.1)	67.3 (13.5)	<0.0001	<0.0001	0.792
Laboratory variables, median [IQR]						
Hb, g/dL	14.0 [13.0-15.0]	14.0 [13.0-15.0]	13.0 [12.0-14.0]	0.020	<0.0001	0.001
Creatinine, mg/dL	0.90 [0.80-1.03]	0.99 [0.84-1.17]	1.13 [0.90-1.48]	<0.0001	<0.0001	<0.0001
Total cholesterol, mg/dL	150.0 [128.0-179.0]	147.0 [127.0-173.0]	145.0 [122.0-169.0]	0.063	0.002	0.092
LDL cholesterol, mg/dL	82.0 [64.0-108.0]	81.0 [64.0-101.0]	78.0 [61.0-98.5]	0.148	0.004	0.055
Triglycerides, mg/dL	113.0 [85.0-154.0]	112.0 [85.0-150.0]	107.0 [79.0-145.0]	0.085	0.009	0.220
Glycaemia, mg/dL	100.0 [90.0-113.0]	106.0 [94.0-128.8]	105.0 [92.0-129.8]	0.175	<0.0001	<0.0001
Uricemia, mg/dL	6.0 [5.0-6.0]	6.00 [4.5-6.0]	6.0 [5.0-8.0]	0.008	0.028	0.472

BMI: body mass index; CABG: coronary artery by-pass grafting; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; Hb: haemoglobin; HR: heart rate: LDL: low density lipoprotein; MI: myocardial infarction; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; TIA: transient ischemic attack.

*ClCr <60 ml/minute, ** Defined as FE < 30% or NYHA Class III or IV

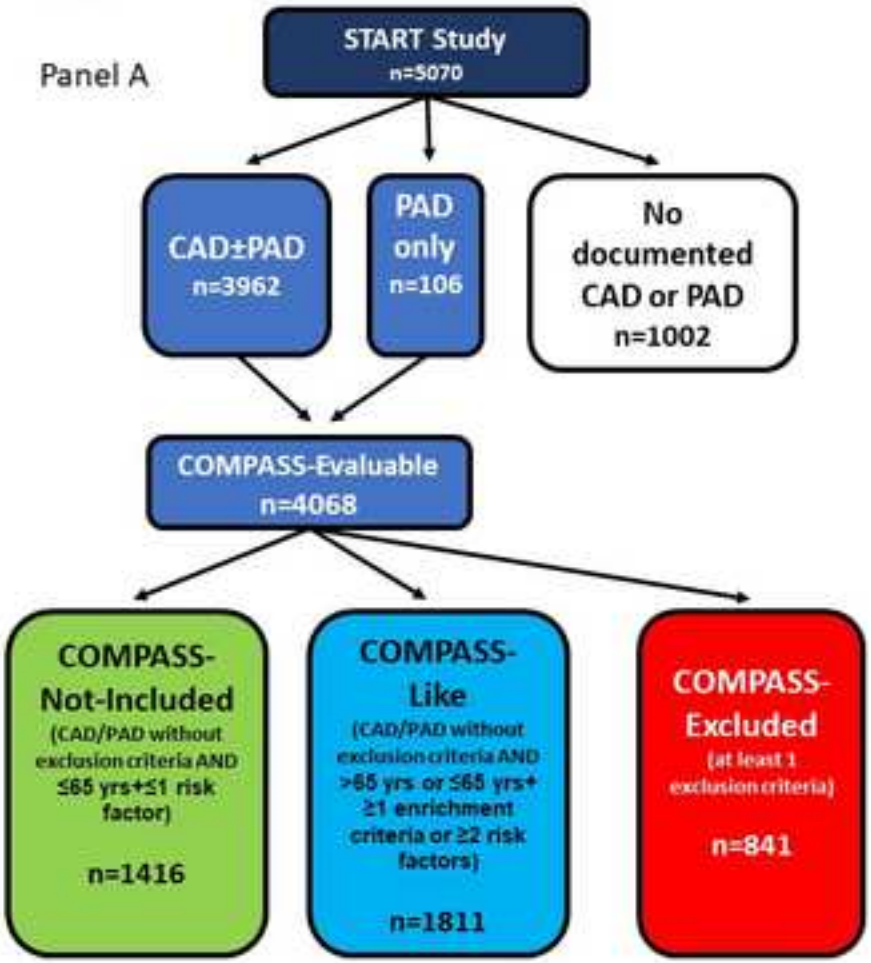
TABLE 2. Pharmacological therapies prescribed in the 3 groups.

	COMPASS NOT-INCLUDED N=1416	COMPASS LIKE N=1811	COMPASS EXCLUDED N=841	P values		
				Like vs Excluded	Excluded vs Not-Included	Like vs Not-Included
ASA, n (%)	1318 (93.1%)	1670 (92.2%)	621 (73.8%)	<0.0001	<0.0001	0.4
Statins, n (%)	1360 (96.0%)	1734 (95.7%)	745 (88.6%)	<0.0001	<0.0001	0.7
Beta-blockers, n (%)	1141 (80.6%)	1396 (77.1%)	661 (78.6%)	0.4	0.3	0.016
ACE-I, n (%)	833 (58.8%)	980 (54.1%)	438 (52.1%)	0.3	0.002	0.007
ARB, n (%)	240 (16.9%)	489 (27.0%)	221 (26.3%)	0.7	<0.0001	<0.0001
Diuretics, n (%)	204 (14.4%)	543 (30.0%)	504 (59.9%)	<0.0001	<0.0001	<0.0001
Calcium antagonists, n (%)	220 (15.5%)	421 (23.2%)	166 (19.7%)	0.04	0.010	<0.0001
MRA, n (%)	56 (4.0%)	148 (8.2%)	230 (27.3%)	<0.0001	<0.0001	<0.0001
Nitrates, n (%)	84 (5.9%)	223 (12.3%)	128 (15.2%)	0.04	<0.0001	<0.0001
Ranolazine, n (%)	1199 (8.4%)	244 (13.5%)	94 (11.2%)	0.09	0.03	<0.0001
Ivabradine, n (%)	104 (7.3%)	118 (6.5%)	68 (8.1%)	0.1	0.5	0.4
OAT, n (%)	50 (3.5%)	35 (1.9%)	313 (37.2%)	<0.0001	<0.0001	0.005
Amiodarone, n (%)	23 (1.6%)	52 (2.9%)	146 (17.4%)	<0.0001	<0.0001	0.02
OMT (overall)	1077 (76.1%)	1329 (73.4%)	499 (59.3%)	<0.0001	<0.0001	0.08
OMT (eligible population)	824 (58.2%)	1075 (59.4%)	383 (45.5%)	<0.0001	<0.0001	0.5

ACE-I: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; ASA: acetylsalicylic acid; MRA: mineralocorticoid receptor antagonist; OAT: oral anticoagulant therapy; OMT: optimal medical therapy

fig 1

FIG. 1



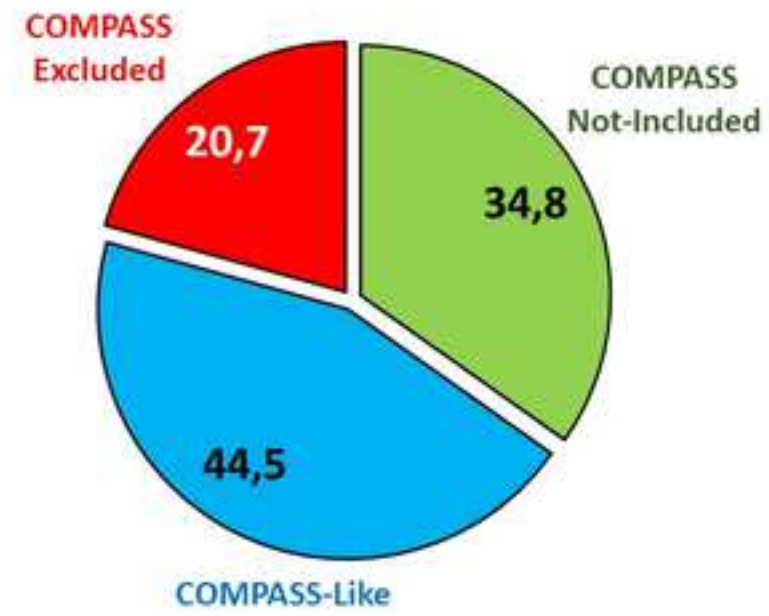


fig 2

FIG. 2

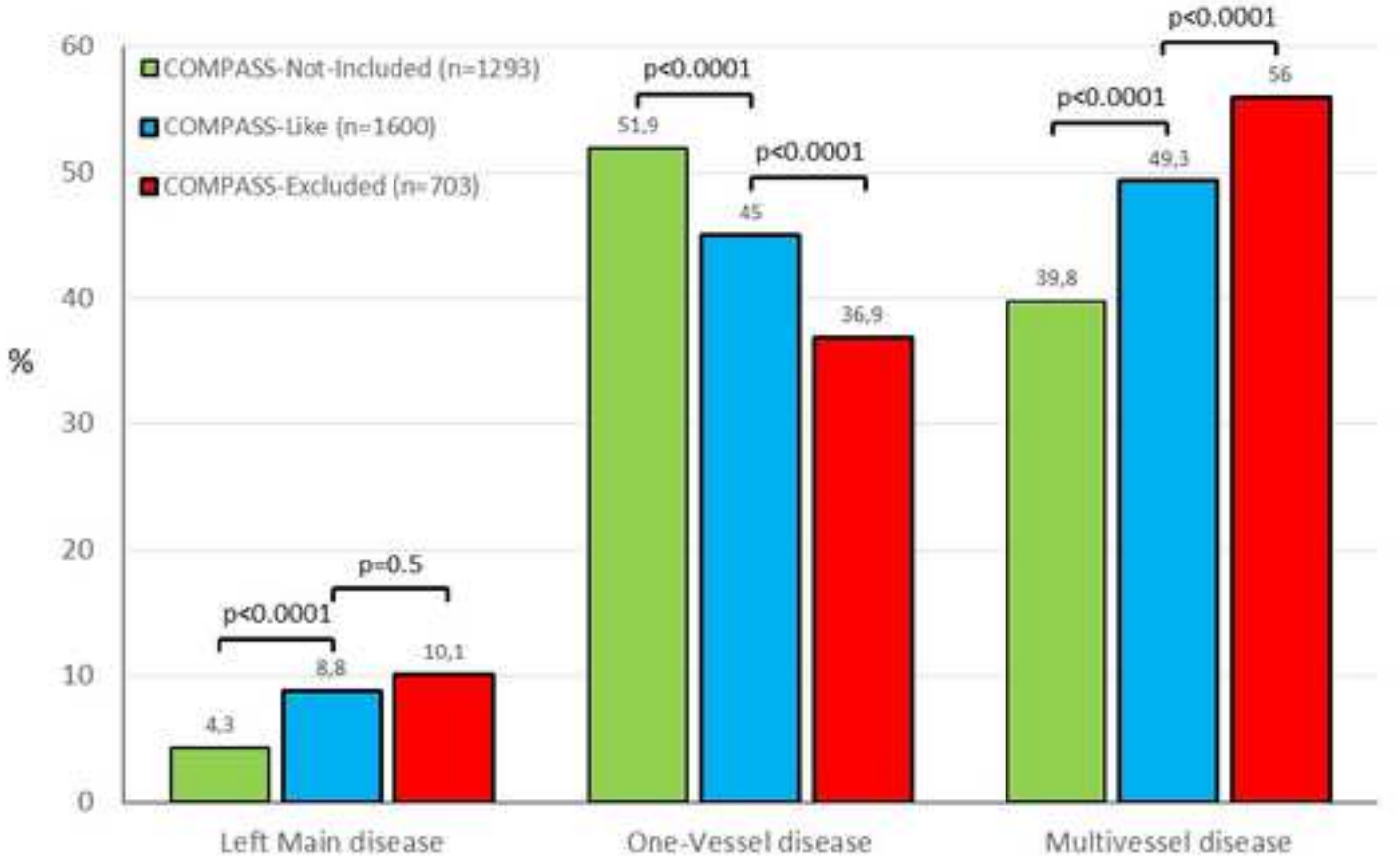


fig 3

FIG. 3

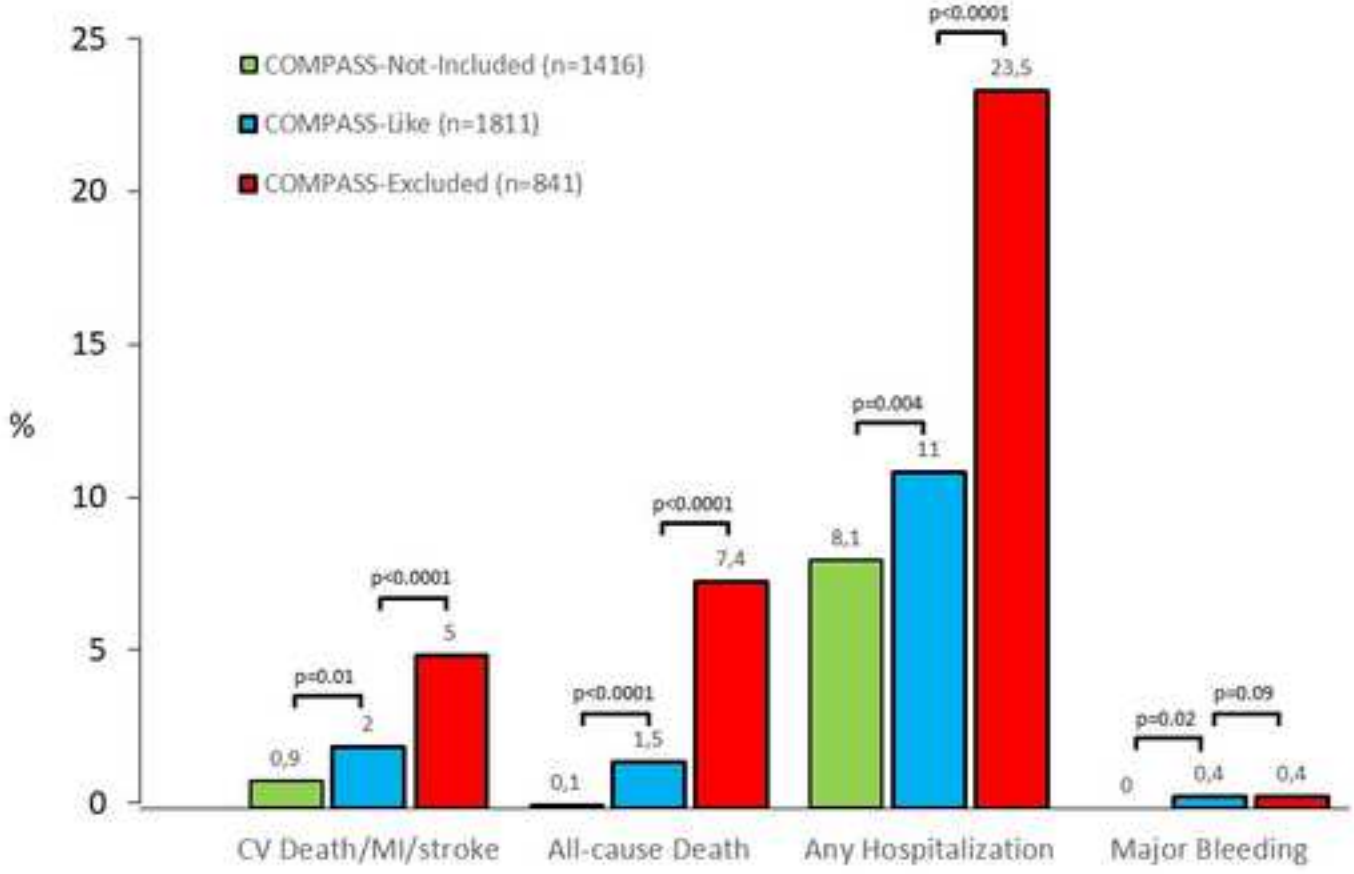


Figure 4

FIG. 4