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The FAST-MI 2005-2010-2015 registries in the light of the COMPASS trial: The COMPASS criteria applied to a post-MI population

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ABSTRACT

Background: The COMPASS trial assessed the impact of adding low dose rivaroxaban to aspirin in selected patients (pts). After an acute myocardial infarction (MI), when dual antiplatelet treatment is no longer needed, patients might be eligible for aspirin/rivaroxaban co-therapy. The characteristics and risks of such a population are unclear.

Methods: Data were extracted from the FAST-MI 2005, 2010 and 2015 nationwide French registries. Characteristics and long-term mortality were compared according to COMPASS eligibility and between registry and trial populations.

Results: Among 9954 patients alive and free of events at one year, 4402 (44%) were classified as COMPASS-Like (i.e. meeting COMPASS inclusion and without exclusion criteria), 1720 (17%) COMPASS-Excluded (i.e. meeting any exclusion criterion) and 3832 (39%) Non-COMPASS (i.e. meeting neither COMPASS inclusion nor exclusion criteria). COMPASS-Like patients were at higher risk and had higher 5-year mortality compared with Non-COMPASS patients. COMPASS-Excluded patients had the highest mortality. COMPASS enrichment criteria defined a population at increased risk of death: eligible pts. had 40% higher 5-year adjusted mortality (Hazard Ratio = 1.40 [1.15; 1.70]), while excluded pts. had 57% higher risk (Hazard Ratio = 1.57 [1.25; 1.97]). Patients meeting the COMPASS criteria one year after MI differed from those included in the randomized trial.

Conclusions: Based on the population included in the French FAST-MI registries, enrichment criteria used in COMPASS defined a population representing 44% of the overall population of MI patients surviving to one year, and these patients are at high risk of 5-year mortality. They were at higher risk compared to chronic stable vascular patients enrolled in the trial.

Registered with Clinicaltrials.gov under the number: NCT00673036.

1. Introduction

Data from a multinational registry show that in Europe, cardiovascular disease makes a considerable contribution to potential years of life lost, accounting for 11 to 39% depending on the country [1]. Declines in mortality, over time, have been observed after acute myocardial infarction (MI), partially explained by more effective treatments [2] but MI patients remain at high residual risk of recurrent ischemic event, even beyond the first year [3]. Among available effective therapies, dual antiplatelet therapy (DAPT) is usually recommended for one year [4–6] and continuation of DAPT for longer than 12 months may be considered [7–10]. Since these strategies with increased or prolonged antithrombotic therapy expose patients to a risk of bleeding complications and do not provide survival advantage, the selection of patients in terms of ischemic and hemorrhagic risk is garnering increasing interest.

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In this context, the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial tested the combination of low-dose aspirin with low-dose (2.5 mg BID) rivaroxaban in chronic stable patients with established atheromatous disease, including a large proportion of patients with previous MI [11]. For patients in COMPASS with a prior MI, half (49.9%) had the MI >5 years prior to randomization [12]. Patient selection in COMPASS aimed to exclude patients at high bleeding risk, and include those at high ischemic risk, based on "enrichment" criteria [13]. The COMPASS trial reported a 24% relative risk reduction (1.3% absolute reduction) in the triple endpoint of cardiovascular death, myocardial infarction and stroke, at the price of an excess of major bleedings (using a modified ISTH bleeding definition that includes hospitalization or emergency room attendance for bleeding), but with a net clinical benefit [11].

Translation of evidence from randomized clinical trials to routine practice is a challenge, since populations included in clinical trials usually do not have the same risk level as real life patients [14–16], and this may alter the risk and benefit of new strategies [17]. One year after MI, patients might be considered for the COMPASS strategy, but patient eligibility, as well as the actual risk level of eligible patients are not clearly defined. To address these questions, we applied the eligibility for COMPASS of participants with a history of MI to an unselected cohort of patients in France with previous MI to determine the proportion of patients who would be eligible for the COMPASS strategy, and determined their actual ischemic and bleeding risk, and long term mortality.

2. Methods

2.1. The FAST-MI cohorts

Data for this population-based cohort study were extracted from three nationwide French registries, conducted 5 years apart, namely FAST-MI 2005 (NCT00673036) [18], FAST-MI 2010 (NCT01237418) [19] and FAST-MI 2015 (NCT02566200) [20]. All registries consecutively included patients with AMI admitted to a coronary or intensive care unit within 48 h of symptom onset, over a one-month period (October–November 2005, 2010 and 2015); for diabetic patients, inclusions were extended for two months in 2005. Data on baseline characteristics, including demographics, risk factors, medical history, use of cardiac procedures, acute management, including timing of reperfusion, use of medications and biological variables were collected, as previously described [21]. Centralized follow-up was performed by the French Society of Cardiology. Dedicated research technicians contacted both physicians and patients, after checking the patients' vital status in municipal registers. All institutions admitting patients for AMI were invited to participate, including university teaching hospitals, community hospitals, and private clinics. The study was conducted in accordance with the guidelines on good clinical practice and French legislation. All three registries were approved by Committees for the Protection of Human Subjects in Biomedical Research. All patients provided written informed consent.

The flowchart of the study population is presented in Supplementary Fig. S1.

2.2. Eligibility analysis

For the eligibility analysis in the present study, we selected patients who were alive at one-year post MI (all three cohorts) and who had not had recurrent MI or stroke during the first year (for FAST-MI 2005 and 2010). For the analysis of risk, only patients suitable for long term (i.e. >12 months after admission) follow-up were considered.

According to the design of the COMPASS trial [13], patients with previous MI were eligible, providing they had additional enrichment (or were older than 65 years) and no exclusion criteria. The exclusion criteria were a "high bleeding risk", heart failure with LVEF < 0.30, end stage renal dysfunction with estimated glomerular filtration rate (eGFR) < 15 ml/min with the CKD-*epi* formula, or the need for DAPT or oral anticoagulant. The COMPASS trial did not further specify who was at high risk or who required DAPT. To address this, we selected patients who had received DAPT for at least one year without a bleeding event. Patients under the age of 65 years were eligible only if they also had PAD or 2 additional enrichment criteria from among the following five: smoking within one year, diabetes, heart failure, previous stroke or mild renal dysfunction defined as eGFR between 15 and 60 ml/min. Due to one or more missing variables, 13% of the patients were classified as "Undetermined" and excluded from the analyses. Remaining patients were classified into three groups: "COMPASS-Like" (i.e. patients fulfilling the inclusion criteria and without exclusion criteria); "COMPASS-Excluded" (i.e. patients with one or more exclusion criteria) and "Non-COMPASS" (i.e. patients with neither inclusion nor exclusion criteria). The combination of enrichment and exclusion criteria across groups is presented using four-ring Venn Diagrams.

2.3. Ischemic and bleeding risk analyses

Ischemic risk was compared across group by comparison of the baseline characteristics at the time of the acute MI, including three risk scores: the Global Registry of Acute Coronary Events (GRACE) [22], the REduction of Atherothrombosis for Continued Health ischemic (REACH) ischemic, threshold ≥ 10 [23] and the Duration of dual antiplatelet therapy after drug-eluting stents (DAPT) score, threshold ≥ 2 [24] risk scores. Eligibility to the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction (PEGASUS) trial [9] was also considered as a high ischemic risk criterion. Bleeding risk was estimated using 4 bleeding risk scores: (1) Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA

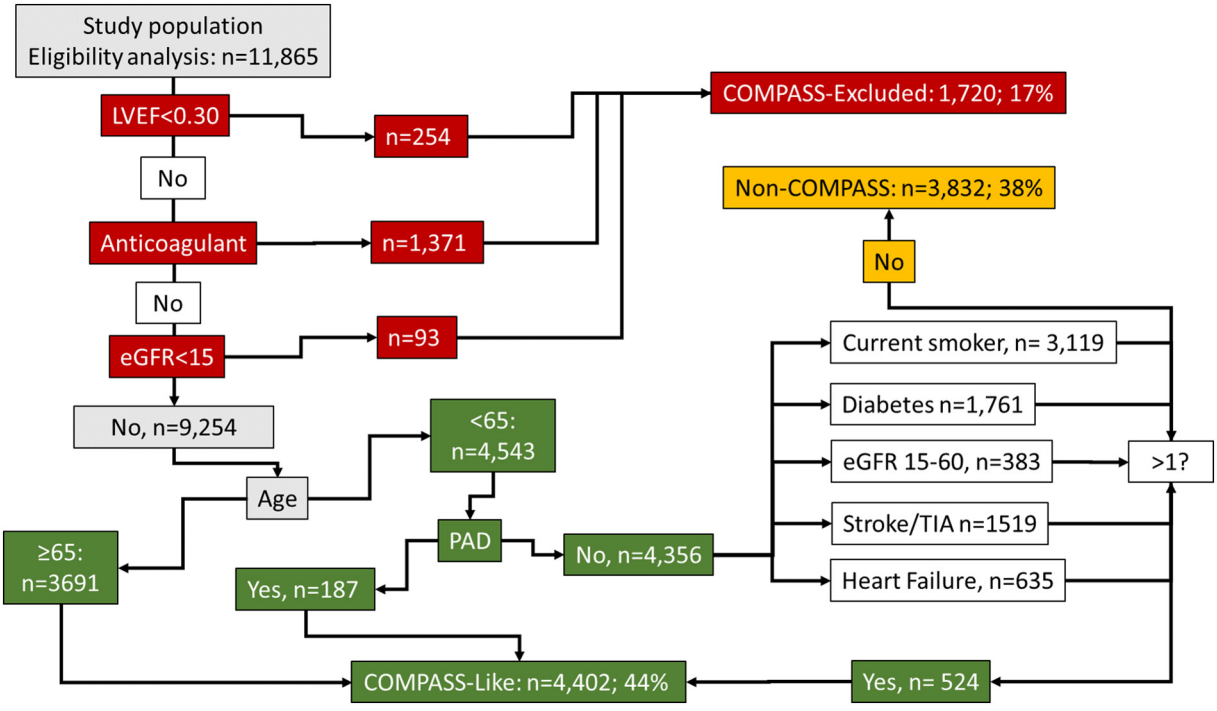

Fig. 1. Detection of eligibility for the COMPASS strategy in patients with previous (>12 months) MI.

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Guidelines (CRUSADE), with a threshold to define high bleeding risk of >20, (2) REACH bleeding score, threshold ≥ 10 [25], DAPT score < 2 [24,25] and PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy (PRECISE-DAPT) score, threshold > 25 [26]. The proportion of COMPASS-Like and Non-COMPASS patients considered at "high ischemic" and "high bleeding" risk, according to the above bleeding and ischemic scores was calculated.

2.4. Outcome analysis

Clinical outcomes were major ischemic cardiac events (all-cause death, recurrent MI or stroke), bleeding requiring medical assistance or hospitalization and all-cause mortality occurring between one and five years after MI. These outcomes were compared between the Non-COMPASS, COMPASS-Like and COMPASS-Excluded groups, without adjustment, using Kaplan-Meier curves and the log Rank test. An additional Cox model, adjusted for deciles of the GRACE risk score [22] was used for multivariate analysis. Characteristics and outcomes at 35 months (i.e. 12 months after acute MI, plus 23 months, median follow-up duration in the COMPASS trial) were compared between COMPASS-Like patients and the actual COMPASS trial population with CAD [12].

3. Statistical analysis

Continuous variables are described as mean ± standard deviation, or as median and interquartile range. Categorical variables are described using absolute and relative frequency distributions. Comparisons were performed between groups two-by-two (Non-COMPASS vs COMPASS-Like, Non-COMPASS vs COMPASS-Excluded, COMPASS-like vs COMPASS-Excluded) using the unpaired *t*-test, or non-parametric Mann-Whitney test for continuous variables, and the chi squared test for discrete variables. Agreement between scores categories and COMPASS criteria (inclusion and non-inclusion) were tested using the Kappa coefficient and 95% confidence interval. The Log Rank test and Cox regression were used for the comparison of outcomes. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). All tests were two sided, and a p value < 0.05 was considered significant.

4. Results

4.1. Eligibility analysis

A total of 11,865 patients were eligible for this analysis, 3147 from FAST-MI 2005, 3813 from 2010 and 4905 from 2015. The 1911(13%) patients who could not be categorized due to missing data had similar baseline characteristics to those of the overall population of the study (mean age 66 ± 14 years, 28% diabetes, average LVEF 52 ± 10% and mortality rate at 5 years 17.9%; Supplementary Table 1). A 3-step algorithm was used to determine patient eligibility (Fig. 1):

Table 1
Baseline characteristics according to the COMPASS eligibility criteria.

Variables N = 11,865 N = 9954	Non-COMPASS N = 3832 (32%) N = 3832 (38%) a	COMPASS-like N = 4402 (37%) N = 4402 (44%) b	COMPASS-Excluded N = 1720 (14%) N = 1720 (17%) c	Undetermined N = 1911 (16%)	P value a vs b	P value b vs c	P value a vs c
Male Gender	3167 (83%)	2893 (66%)	1180 (69%)	1331 (70%)	<0.001	0.03	0.03
Age (years)	54 (8)	73 (10)	72 (11)	71 (14)	<0.001	0.07	<0.001
Age > 75 years	0	1941 (44%)	796 (46)	606 (32%)	<0.001	0.13	<0.001
Age ≥ 65 years	0	3691 (84%)	1253 (73%)	1021 (53%)	<0.001	<0.001	<0.001
STEMI	2429 (63%)	2110 (48%)	793 (46%)	921 (48%)	<0.001	0.20	0.74
Hypertension	1302 (34%)	2879 (65%)	1138 (66%)	1073 (56%)	<0.001	0.57	<0.001
Hypercholesterolemia	1474 (38%)	2176 (49%)	810 (47%)	855 (45%)	<0.001	0.10	<0.001
Current smokers	2115 (55%)	1004 (23%)	371 (22%)	609 (32%)	<0.001	0.30	<0.001
Diabetes mellitus	307 (8%)	1462 (33%)	530 (31%)	537 (28%)	<0.001	0.07	0.02
History of stroke	0	383 (9%)	171 (10%)	114 (6%)	<0.001	0.13	0.07
Recurrent MI	355 (9%)	830 (19%)	429 (25%)	374 (20%)	<0.001	<0.001	0.05
History of heart failure	12 (0.3%)	194 (4%)	191 (11%)	118 (6%)	<0.001	<0.001	<0.001
Peripheral artery disease	0	547 (12)	203 (12%)	145 (8%)	<0.001	0.50	<0.001
Atrial Fibrillation	0	0	935 (54%)	182 (10%)	<0.001	<0.001	<0.001
GRACE risk score	118 (24)	151 (30)	162 (36)	141 (35)	<0.001	<0.001	<0.001
CRUSADE risk score	16 (10)	33 (14)	36 (16)	29 (16)	<0.001	0.001	<0.001
REACH ischemic score	9.2 (3.1)	12.4 (3.3)	13.8 (4.3)	11.4 (4.0)	<0.001	<0.001	<0.001
REACH bleeding score	3.8 (1.7)	7.5 (2.6)	10.7 (3.0)	7.3 (3.2)	<0.001	<0.001	<0.001
DAPT score	1.74 (0.57)	0.56 (13)	0.74 (1.3)	1.1 (1.2)	<0.001	<0.001	<0.001
PRECISE-DAPT score	11.5 (5.9)	25.5 (10.1)	27.3 (11.7)	22.0 (12.6)	<0.001	<0.001	<0.001
PEGASUS criteria							
Non-Inclusion	1250 (13)	140 (1)	91 (1)	243 (3)			
Inclusion	520 (5)	3338 (35)	977 (10)	1102 (12)	<0.001	<0.001	<0.001
Exclusion	216 (2)	783 (8)	475 (5)	277 (3)			
LVEF %	55 (9)	55 (10)	46 (14)	52 (10)	0.68	0.68	<0.001
LVEF <0.40	375 (10%)	719 (16%)	627 (36%)	38 (2%)	<0.001	<0.001	<0.001
LVEF <0.30	0	0	1466 (85%)	279 (15%)			
Haemoglobin (mg/dL)	14.7 (1.5)	13.7 (1.8)	13.5 (1.9)	13.7 (1.8)	<0.001	0.01	<0.001
eGFR (CKD-EPI) (ml/min)	92 (16)	69 (21)	64 (25)	73 (24)14%	<0.001	0.001	<0.001
eGFR CKD-EPI > 90 ml/min	2269 (59%)	746 (17%)	276 (16%)	425 (27%)			
eGFR CKD-EPI 60–90 ml/min	1482 (37%)	2218 (50%)	732 (43%)	660 (42%)	<0.001	<0.001	<0.001
eGFR CKD-EPI 30–60 ml/min	79 (2%)	1276 (29%)	541 (30%)	401 (26%)			
eGFR CKD-EPI 15–30 ml/min	2 (0.5%)	162 (4%)	78 (5%)	48 (3%)			
eGFR CKD-EPI <15 ml/min	0	0	93 (5%)	24 (1.5%)			

STEMI, ST elevation myocardial infarction; FMC, first medical contact; h, hours; PCI, percutaneous coronary intervention; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; COPD, chronic obstructive pulmonary disease; BP, blood pressure; GRACE [22]: Global Registry of Acute Coronary Events; CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines; REACH: The REduction of Atherothrombosis for Continued Health ischemic [23], bleeding [25]; DAPT [24]: Duration of dual antiplatelet therapy after drug-eluting stents; PRECISE-DAPT: PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy [26]; PEGASUS: Eligibility to the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction [9] LVEF, left ventricular ejection fraction; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease. *: comparison between Non-COMPASS and COMPASS-like; **: comparison between COMPASS-like and COMPASS-Excluded.

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- Check for exclusion criteria: chronic anticoagulation, impaired LV function with LVEF < 0.30 or severe renal dysfunction (eGFR<15 ml/min).
- Check for inclusion criteria: age ≥ 65 or history of PAD
- Check for two enrichment criteria among remaining patients.

In the "COMPASS-Excluded" group ($n = 1720$, 17%) the main exclusion criterion was chronic anticoagulation, followed by impaired LV function with LVEF<0.30 and severe renal dysfunction (eGFR < 15 ml/min). In the "COMPASS-Like" group ($n = 4402$, 44%), 84% were ≥65 years, 4% had PAD, and 12% were <65 years with two (or more) enrichment criteria. The most common enrichment criteria were diabetes + smoking and diabetes + renal dysfunction (Supplementary Fig. S2). The remaining "Non-COMPASS" patients ($n = 3832$, 39%) had no inclusion and no exclusion criteria. The baseline characteristics of these groups are presented in Table 1 and their management during index hospitalization and discharge treatment presented in Table 2.

4.2. Ischemic risk

Compared to the "Non-COMPASS" group, the COMPASS-Like group had more severe baseline characteristics with regard to age, previous disease, risk factors and renal dysfunction. The differences in baseline characteristics were less pronounced between the COMPASS-Like and COMPASS-~~Excludedgroups~~, but patients from the COMPASS Excluded group had higher ischemic and bleeding risks, as assessed by the GRACE and CRUSADE scores.

4.3. Bleeding risk

Whatever the score considered, bleeding risk was lowest in the Non-COMPASS group, followed by the COMPASS-Like group and lastly, the COMPASS-Excluded group. Similar results were observed when score values were transformed into categories, according to the recommended thresholds.

The overlap between PEGASUS criteria, ischemic and bleeding scores showed that COMPASS inclusion criteria selected a large proportion of high ischemic risk (PEGASUS-Like, REACH-ischemic > 10, DAPT score ≥ 2) and low bleeding risk (CRUSADE ≤ 20, DAPT < 2) patients, even if the agreement between COMPASS criteria and scores was modest, according to the Kappa coefficient (Fig. 2).

4.4. Outcomes analysis

In the FAST-MI 2005 and 2010 cohorts, the mortality rate at five years was twofold higher in the COMPASS-Like (411/2086, 16.5%) than in the Non-COMPASS group (184/1900, 8.8%, $p < 0.001$), and lower than that of the COMPASS-Excluded group (194/805, 19.5%, $p = 0.045$) (Fig. 3). After adjustment for deciles of the GRACE risk score, the higher mortality risk was confirmed for the COMPASS-Like versus Non-COMPASS groups (HR = 1.40 [1.15; 1.70]) and for the COMPASS-Excluded versus Non-COMPASS groups (HR = 1.57 [1.25; 1.97]). Similar results were observed for the comparison of the risk of death, recurrent MI or stroke between 1 and 5 years.

The comparison of registry patients with the clinical trial population showed that COMPASS-Like patients had higher risk characteristics than those included in the COMPASS trial, either the whole population [11] or the COMPASS patients with previous coronary artery disease [12]. The use of guidelines-recommended treatments was high in all patients, but lower in the "COMPASS-Like" than in the "Non-COMPASS" group. There were differences in the rates of beta-blocker and ACEI use (lower in the COMPASS trial (whole population and CAD population) than in the FAST-MI population), but the rates of aspirin and statin use were comparable. A twofold higher rate of all-cause mortality was observed in the COMPASS-Like group (8.5%) as compared to the Rivaroxaban + aspirin group (3.3%, $p < 0.001$) in the COMPASS trial, and vs 4.1% in the control group (4.0% in COMPASS-CAD placebo group) ($p < 0.001$) (Supplementary Table 1).

Adjustment for deciles of the GRACE risk score (Supplementary Fig. S3), or for quartiles of the GRACE, CRUSADE, and REACH ischemic scores did not alter the results.

5. Discussion

One year after an acute MI, patients are no longer considered as "unstable", according to guidelines, the DAPT might be stopped and these patients might be eligible for the addition of low-dose rivaroxaban to aspirin, according to the specific inclusion and exclusion criteria of the COMPASS trial. Our results show that, when applied to a "real-life" population of consecutive patients admitted one year previously for acute MI, 44% of patients were classified "COMPASS-Like", 17% were COMPASS-Excluded and 38% were Non-COMPASS (i.e. with neither inclusion nor exclusion criteria).

External validity of the results of randomized trials is challenging [15], because in clinical studies, the patients are selected according to pre-defined criteria and are often at lower risk than in clinical practice

Table 2
Treatments, procedures and treatments at discharge and 5-year mortality, according to the COMPASS eligibility.

Variables N = 11,865 N = 9954	Non-COMPASS N = 3832 (32%) N = 3832 (38%) a	COMPASS-like N = 4402 (37%) N = 4402 (44%) b	COMPASS-Excluded N = 1720 (14%) N = 1720 (17%) c	Undetermined N = 1911 (16%)	P value a vs b	P value b vs c	P value a vs c
STEMI with FMC <12 h	2275 (94%)	1997 (93%)	720 (93%)	854 (93%)	0.12	0.20	0.86
Reperfusion among eligible patients	1962 (81%)	1470 (70%)	512 (65%)	688 (75%)	<0.001	0.008	<0.001
Aspirin at discharge	3716 (97%)	4196 (96%)	1486 (89%)	1742 (93%)	0.008	<0.001	<0.001
Dual antiplatelet therapy at discharge	3498 (94%)	3721 (89%)	1143 (77%)	1552 (89%)	<0.001	<0.001	<0.001
Clopidogrel at discharge	1532 (40%)	2407 (55%)	1000 (60%)	1135 (61%)	<0.001	<0.001	<0.001
Prasugrel at discharge	980 (26%)	444 (10%)	97 (6%)	230 (12%)	<0.001	<0.001	0.76
Ticagrelor at discharge	1048 (27%)	972 (22%)	129 (7%)	262 (14%)	<0.001	<0.001	<0.001
Chronic beta blocker use	3378 (89%)	3656 (84%)	1335 (80%)	1479 (80%)	<0.001	<0.001	<0.001
Chronic ACEI/ARB use	2945 (77%)	3387 (78%)	1226 (73%)	1290 (70%)	0.44	<0.001	<0.001
Chronic statin use	3603 (93%)	3926 (90%)	1407 (84%)	1625 (88%)	<0.001	<0.001	<0.001
Chronic Anticoagulation	0	0	1371 (80%)	280 (15%)	<0.001	<0.001	<0.001
1–5 years death, recurrent MI or Stroke	254/2084 (12.2%)	527/2497 (21.1%)	237/999 (23.4%)	302/1379 (21.9%)			
1–5 year Bleeding	2/797 (0.25%)	15/1124 (1.3%)	10/470 (2.1%)	9/756 (1.2%)			
1–5 years All Cause mortality	184 (8.8%)	411 (16.5%)	199 (19.4%)	247 (17.9%)	<0.001	0.08	<0.001

Same abbreviations as in Table 1. STEMI, ST elevation myocardial infarction.

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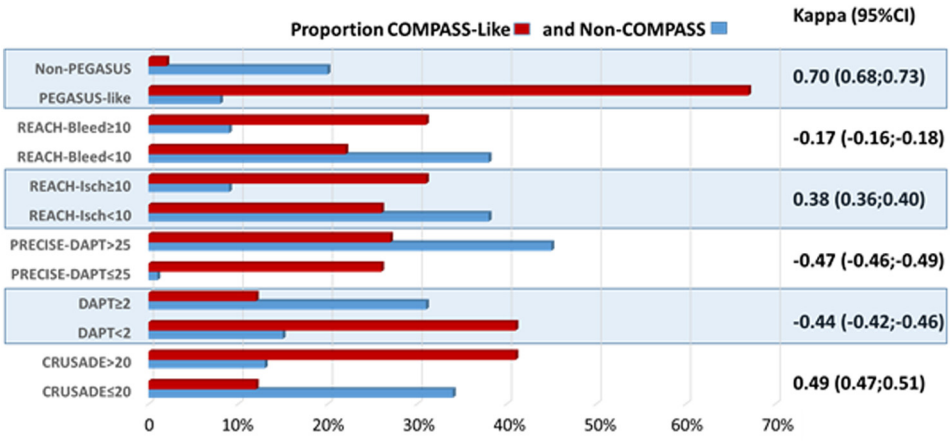

Fig. 2. Overlap between COMPASS criteria (inclusion and non-inclusion) and PEGASUS criteria, REACH ischemic and bleeding scores, PRECISE-DAPT and CRUSADE scores.

[14,27,28]. Our results confirm that post MI patients in clinical practice are at higher risk of subsequent CV events that those enrolled in COMPASS. The COMPASS-like population had more high risk characteristics than the randomized trial population and mortality after 35 months was almost twice that reported in the control arm of the COMPASS study (8.5% versus 4.0%), consistent with observations from previous studies [28–30]. This suggests that the clinical benefit of the COMPASS strategy could be greater in a real-life population than that observed in the trial, with a reduction of the "number needed to treat".

Previous studies have shown that an increase in intensity of antithrombotic treatment might reduce ischemic events, but at the price of more bleeding complications [9,31–34]. Thus, exclusion of "high bleeding risk" patients for these strategies is a major issue. In the FAST-MI population, 17% of the patients had a COMPASS-exclusion criterion, mainly the need for chronic anticoagulation. In line with previous observations, the patients with exclusion criteria also had high-risk baseline characteristics and actually had the highest long term mortality [16,17,30]. When applied to the REACH registry population, a higher proportion (29.8%) was "COMPASS-Excluded", as compared to 17% in FAST-MI. This difference is explained by the addition of a bleeding score to exclude patients. In our study, the patients had all been treated for 12 months with DAPT without bleeding events. Previous studies have reported that, under DAPT [35], the excess of bleeding, if any, frequently occurs early after initiation, and less frequently thereafter. Detecting patients at low bleeding risk in this manner has certain limitations, as shown in the DAPT trial where, despite inclusion of patients treated with DAPT for 12 months without bleeding events, an excess of hemorrhagic complications was observed in the extended DAPT arm [33]. In COMPASS, bleeding was "front loaded", most occurring in the first year of the study [12]. This suggests that the "bleeding test" of a year of DAPT without bleeding complications is likely to select a population with lower risks of bleeding than for a chronic stable population without "test exposure". Nevertheless, we cannot rule out the possibility that some patients might not tolerate low dose rivaroxaban, despite having been treated with DAPT for one year without bleeding event. In the COMPASS trial, the proportion of patients screened and finally excluded after the run-in period was low, at only 3.1%.

In addition to this bleeding risk test, the selection of patients post MI has other advantages. As compared to patients with PAD, post MI patients are more numerous and the 12-month follow-up visit is usually planned for cessation or prolongation of the DAPT. Reviewing such patients at the end of DAPT gives an opportunity for the clinician to consider whether the patients may benefit from the COMPASS regimen. Much later, stable vascular patients will be more difficult to identify in many countries as they may no longer be under specialist review. Additionally, candidates for the COMPASS regimen can be identified earlier, just after the end of DAPT. As shown in the DAPT, CRUSADE, PRECISE-DAPT or REACH-Bleeding scores, older age is regularly associated with increased bleeding risk. This was also observed in the COMPASS study where, despite no significant interaction with age, major bleedings were numerically more frequent with older age [12]. In the COMPASS Trial, in patients <65 years, the absolute reduction in ischemic events with Rivaroxaban 2.5 mg bid versus placebo was 2.4% with only 0.12% increase in major bleeding event. As a result, this subgroup yielded

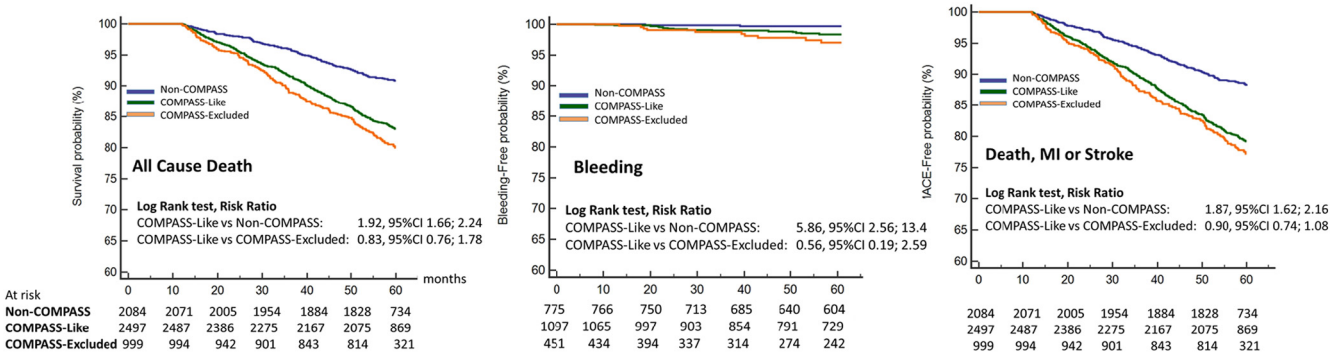

Fig. 3. Kaplan-Meier curves for 1 to 5-years, among survivors without event at one year, for all-cause mortality (left panel), major bleeding (middle panel) and major ischemic events (all-cause death, recurrent MI and stroke) (right panel) according to the COMPASS groups.

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the highest net clinical benefit (absolute value 2.4%) from the addition of 2.5 mg bid of rivaroxaban [11]. In our study, COMPASS-Like patients <65 years represented 12% of the COMPASS-Like group and 4.4% of the whole post MI population.

Based on an estimated annual incidence of MI of 225/100,000 inhabitants in 2012 in Denmark [36], applied to the Western European level (397.10^6 inhabitants), with 10% mortality during the first year, the 44% of COMPASS-eligible patients would represent 353,727 patients per year. Considering the mortality and major bleeding rates observed in FAST-MI from 1 to 5 years (12.3% and 1.3% respectively), as well as the relative reduction in mortality (HR = 0.77) and the increase in bleeding (HR = 1.66) observed in COMPASS CAD [12], then the number of deaths prevented in Europe after 4 years of treatment would be 10,223 (i.e. 33,285 instead of 45,508), at the cost of an excess of 3035 non-fatal major bleeds.

Lastly, the "Non-COMPASS" group represented 38% of the population, without COMPASS inclusion or exclusion criteria. In the FAST-MI population, Non-COMPASS patients were at low risk, not only according to baseline characteristics, age and existing ischemic and bleeding scores, but confirmed by the high event-free survival at 4 years. Whether these patients would benefit from more intense antithrombotic treatment remains to be determined.

6. Study strengths and limitations

Our study suffers the same limitations as all observational studies: namely, no causality can be asserted between parameters that are correlated. The population from the three FAST-MI registries represents a nationwide sample in France, but cannot necessarily be extrapolated to other countries. The selection of a population who had an MI 12 months previously does not correspond to the population of the COMPASS trial; although 69% in the COMPASS trial had a previous MI, half of the MIs had occurred >5 years before inclusion in the trial. In addition, some patients were treated 12 years previously, which could modify the long-term risk, even if the population had a similar high rate of guidelines-recommended treatment to that in the COMPASS trial. Furthermore, there was a run-in period in the COMPASS trial, after which 3.1% of patients were excluded. We were unable to take the run-in period into account in this analysis from the FAST-MI registries. Finally, one year after an acute MI, some patients could qualify for prolonged DAPT, for example with ticagrelor 60 mg twice daily, which would exclude them from the COMPASS regimen.

7. Conclusions

In clinical practice, applying the COMPASS inclusion and exclusion criteria to a population of one-year survivors without intercurrent bleeding or ischemic event after acute MI, showed that 44% of patients were eligible, 38% non-eligible and 17% contra indicated. The enrichment criteria used in the COMPASS trial succeeded in defining a population at increased risk of death since, compared to non-eligible patients, eligible patients had a 40% higher adjusted mortality and those who were excluded had a 57% higher risk.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.138.

Disclosures

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