Medications Recommended for Secondary Prevention After First Acute Coronary Syndrome: Effectiveness of Treatment Combinations in a Real-Life Setting

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Long-term effectiveness of evidence-based cardiovascular medications (EBCMs) indicated after acute coronary syndrome (ACS) needs to be assessed considering the combination effects for these drugs recommended in association. Using a nationwide database, we conducted a cohort study to evaluate the effectiveness of all possible incomplete EBCMs-based combinations as compared to that associating the four recommended EBCMs over up to 5 years of follow-up. Among the 31,668 patients included, 22.9% had ACS recurrence or died during follow-up. The risks associated with the use of 3-EBCM based combinations were 1.46 (95% confidence interval: 1.33–1.60) for the combinations without statins, 1.30 (1.17–1.43) for the combinations without angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 1.11 (0.98–1.25) for the combinations without antiplatelet agents, and 0.99 (0.89–1.10) for the combination without beta-blockers. These findings question the interest of maintaining long-term treatment with beta-blockers in addition to the other EBCMs for post-ACS secondary prevention.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Evidence-based cardiovascular medications (EBCMs) are indicated after acute coronary syndrome (ACS), but their long-term effectiveness needs to be assessed considering the combination effects of these drugs recommended in association. Effectiveness of beta-blockers in the post-ACS context is disputed, as trials on these drugs were performed long ago and signals of ineffectiveness have emerged from observational studies.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Using a nationwide database, the study addressed the question of the long-term effectiveness of the EBCM combination recommended for secondary prevention after first ACS.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ Regardless of heart function, long-term use of combinations including all EBCMs without beta-blockers did not appear less effective than the full EBCM combination on ACS recurrence or all-cause death. Conversely, for all other EBCM-based combinations, long-term use after ACS was confirmed to be less effective than the full EBCM combination.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

☑ These findings question the interest of maintaining long-term treatment with beta-blockers in addition to the other EBCMs for post-ACS secondary prevention.

Secondary prevention after acute coronary syndrome (ACS) is evidence-based on the combined use of four drug classes: angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), antiplatelet agents (APAs), beta-blockers, and statins.[1–7] These drugs constitute the evidence-based cardiovascular medications (EBCMs) and the full combination associates the four EBCMs, the reference therapy. Several studies evaluated the efficacy of EBCMs in real-life conditions[8–11] that could be affected by noncompliance to treatment encountered in post-ACS.[12–15] These studies, which essentially focused on post-acute myocardial infarction (AMI), did not evaluate the effectiveness of these drugs when used in combination, or apply assessment procedures for drug uses that risked an immeasurable-time bias.[16] Additionally, for some EBCM, e.g., beta-blockers, the evidence relies on clinical trials for AMI that preceded the development of modern strategies for the management of the acute phase of this event.[17–22] The potential interest in these drugs has been recently disputed in post-AMI, especially

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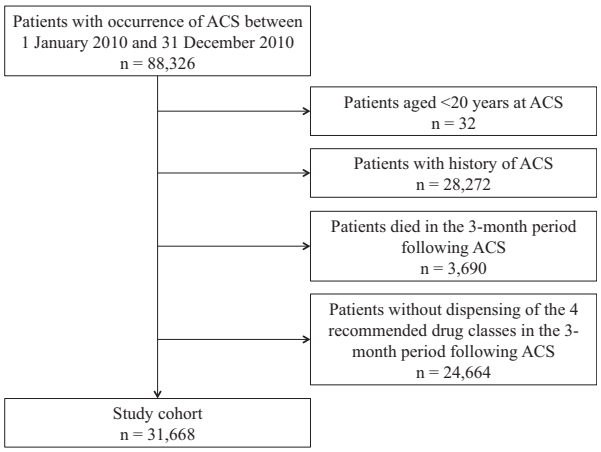

Figure 1 Flow chart of study patient selection identification process.

in patients without heart failure (HF).[23–25] Such evaluation needs to be extended to the general context of post-ACS; in this, the assessment should consider the specificity of the combined use of these EBCMs, which has not been done to date in existing studies, mostly because of power limitations.

Using a nationwide database, we conducted a cohort study to evaluate the effectiveness of all possible incomplete EBCMs-based combinations as compared to that associating the four recommended EBCMs (referred to as the full EBCM combination) over up to 5 years of follow-up.

RESULTS

Patient characteristics

Of the 88,326 patients who experienced an ACS in 2010, 31,668 (35.9%) were incident ACS patients discharged with the full EBCM combination and thus included in this cohort study (**Figure 1**). Over the study follow-up (median duration: 4.1 years; interquartile range, IQR: 3.5–4.4), 7,240 of these (22.9%) presented with a recurrence of ACS or died.

Median age at initial ACS was 65 years (IQR: 55–76); 22,089 patients (69.8%) were male; history of HF was found in 6,403 patients (20.2%), diabetes in 9,792 (30.9%), and hypertension in 19,449 (61.4%). Compared to patients without HF at inclusion, HF patients were older (74 years vs. 63 years) and had more comorbidities: cardiac arrhythmia (46.9% vs. 20.1%), chronic obstructive pulmonary disease (8.1% vs. 2.9%), diabetes (41.3% vs. 28.3%), or hypertension (73.8% vs. 58.3%). Patient baseline characteristics are detailed in **Table 1**.

EBCM exposure

Exposure to the full EBCM combination accounted for 49.4% of follow-up time, exposure to the 3-EBCM-based combination without ACEIs/ARBs 6.1%, exposure to the 3-EBCM-based combination without APAs 4.8%, exposure to the 3-EBCM-based combination without beta-blockers 8.6%, and exposure to the 3-EBCM-based combination without statins 14.2%. These trends of EBCM exposure were similar between HF and non-HF patients.

Effectiveness of EBCM

Compared to the recommended full EBCM combination, use of 3-EBCM-based combinations without statins (adjusted hazard ratio, aHR: 1.46; 95% confidence interval, CI: 1.33–1.60), or without ACEIs/ARBs (1.30; 1.17–1.43) were associated with a higher risk of ACS recurrence or all-cause death. Use of 3-EBCM-based combination without APAs (1.11; 0.98–1.25), or without beta-blockers (0.99; 0.89–1.10) did not modify the risk of ACS recurrence or all-cause death compared to the recommended full EBCM combination (**Table 2**). Results of the effectiveness analysis are summarized in **Figure 2**.

While trends were similar, the increase in the risk of ACS recurrence or all-cause death appeared higher for HF patients after stratifying the analysis according to HF history. In HF patients, the risk associated with the use of the 3-EBCM-based combination without ACEIs/ARBs compared to the full EBCM combination was 1.44 vs. 1.19 in non-HF patients. It was 1.12 for use of the 3-EBCM-based combination without antiplatelet agent vs. 1.07 in non-HF patients. Noticeably in non-HF patients, the use of the 2-EBCM ACEIs/ARBs-statins-based combination was not found to be associated with a specific risk of ACS recurrence or all-cause death compared to the full EBCM combination (1.07; 0.85–1.34; **Table 2**).

Associations differed concerning all-cause mortality. The increased risk associated with the use of the 3-EBCM-based combination without ACEIs/ARBs or without APAs compared to the use of the full EBCM combination was higher for all-cause death than for the combined outcome of ACS recurrence or all-cause death (1.51 vs. 1.30, and 1.18 vs. 1.11, respectively). The increased risk associated with the use of the 3-EBCM-based combination without statins compared to the use of the full EBCM combination was slightly lower (1.30 vs. 1.46). The use of the 3-EBCM-based combination without beta-blockers was still not associated with an increased risk of all-cause death compared to the full EBCM combination (0.97; 0.83–1.13; **Table 3**).

DISCUSSION

Regardless of the heart function, long-term use of combinations including all EBCMs without beta-blockers did not appear less effective than the full EBCM combination on ACS recurrence or all-cause death. These findings question the interest of maintaining long-term treatment with beta-blockers in addition to the other EBCMs for post-ACS secondary prevention.

Thanks to the large database used, this study was able to compare the effectiveness of the full EBCM recommended combination with all possible EBCM combinations in secondary prevention of ACS in real life. Comparing combinations allowed providing an assessment of the effectiveness of individual EBCMs that are missing in incomplete combinations independently of the effect of other EBCMs used. This is especially of interest for combinations based on three of the four recommended EBCMs. Moreover, as only patients discharged after incident ACS with the full EBCM combination were considered in this cohort, bias in findings that could be consecutive to barriers to the prescribing of each and any EBCM can be excluded.

Table 1 Patient characteristics at baseline according to presence of heart failure at inclusion

	Full cohort *N* = 31,668	HF patients *N* = 6,403	Non-HF patients *N* = 25,265
Age at ACS, year, median [IQR]	65 [55;76]	74 [61;81]	63 [54;74]
Gender, female, *n* (%)	9,579 (30.2)	2,485 (38.8)	7,094 (28.1)
Initial ACS characteristics			
Diagnosis of initial ACS, *n* (%)			
Acute myocardial infarction	18,759 (59.2)	4,166 (65.1)	14,593 (57.8)
Unstable angina	11,511 (36.3)	1,956 (30.5)	9,555 (37.8)
Other acute coronary syndrome	1,398 (4.4)	281 (4.4)	1,117 (4.4)
First procedure performed, *n* (%)			
PCI	18,991 (60.0)	3,099 (48.4)	15,892 (62.9)
CABG	654 (2.1)	196 (3.1)	458 (1.8)
Duration of hospitalization, day, median [IQR]	5 [3;7]	7 [4;11]	4 [3;7]
Characteristics in the year before initial ACS, *n* (%)			
Abnormal liver function	480 (1.5)	157 (2.5)	323 (1.3)
Abnormal renal function	2,767 (8.7)	1,368 (21.4)	1,399 (5.5)
Cardiac arrhythmia	8,080 (25.5)	3,002 (46.9)	5,078 (20.1)
Chronic obstructive pulmonary disease	1,244 (3.9)	516 (8.1)	728 (2.9)
Dementia	652 (2.1)	247 (3.9)	405 (1.6)
Diabetes	9,792 (30.9)	2,645 (41.3)	7,147 (28.3)
Heart failure	6,403 (20.2)	—	—
Hypertension	19,449 (61.4)	4,728 (73.8)	14,721 (58.3)
Major hemorrhage	1,773 (5.6)	644 (10.1)	1,129 (4.5)
Neoplasm, benign or in situ	1,083 (3.4)	286 (4.5)	797 (3.2)
Neoplasm, malignant	3,041 (9.6)	784 (12.2)	2,257 (8.9)
Neoplasm, with metastasis	226 (0.7)	68 (1.1)	158 (0.6)
Peripheral artery disease	4,248 (13.4)	1,302 (20.3)	2,946 (11.7)
Stroke, ischemic	513 (1.6)	172 (2.7)	341 (1.3)
Stroke, hemorrhagic or undetermined	593 (1.9)	195 (3.0)	398 (1.6)
Transient ischemic attack	296 (0.9)	91 (1.4)	205 (0.8)
Use of anticoagulant drugs	5,154 (16.3)	1,861 (29.1)	3,293 (13.0)
Use of calcium channel blockers	10,364 (32.7)	2,621 (40.9)	7,743 (30.6)
Use of diuretics	15,372 (48.5)	5,105 (79.7)	10,267 (40.6)
Use of nitrates	16,591 (52.4)	3,045 (47.6)	13,546 (53.6)
Use of other lipid-lowering agents	5,980 (18.9)	1,126 (17.6)	4,854 (19.2)
Characteristics in the 6 months before initial ACS			
Number of different drugs, median [IQR]	9 [4;15]	11 [6;17]	9 [4;14]
Number of medical consultation, median [IQR]	5 [2;8]	5 [3;9]	4 [2;7]
Use of EBCM, *n* (%)			
ACEIs or ARBs	15,616 (49.3)	3,827 (59.8)	11,789 (46.7)
APAs	11,163 (35.3)	2,806 (43.8)	8,357 (33.1)

Table 1 Continued on next page

Table 1 Continued

	Full cohort *N* = 31,668	HF patients *N* = 6,403	Non-HF patients *N* = 25,265
Beta-blockers	10,601 (33.5)	2,614 (40.8)	7,987 (31.6)
Statins	12,181 (38.5)	2,820 (44.0)	9,361 (37.1)
New EBCM users at inclusion, *n (%)*			
ACEIs or ARBs	16,052 (50.7)	2,576 (40.2)	13,476 (53.3)
APAs	20,505 (64.7)	3,597 (56.2)	16,908 (66.9)
Beta-blockers	21,067 (66.5)	3,789 (59.2)	17,278 (68.4)
Statins	19,487 (61.5)	3,583 (56.0)	15,904 (62.9)
Median duration of follow-up, year, median [IQR]	4.1 [3.5;4.4]	3.9 [1.9;4.3]	4.1 [3.8;4.4]
Occurrence of outcome of interest, *n (%)*			
All-cause-death	3,710 (11.7)	1,676 (26.2)	2,034 (8.1)
ACS recurrence or all-cause-death	7,240 (22.9)	2,263 (35.3)	4,977 (19.7)

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; APA, antiplatelet agent; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; HF, heart failure; IQR, interquartile range; PCI, percutaneous coronary intervention.

Table 2 Primary analysis: Association between use of secondary prevention treatment during follow-up and occurrence of ACS recurrence or all-cause death, for the full cohort and stratified on the presence of heart failure at inclusion (Cox model)

	Full cohort		HF patients		Non-HF patients	
	PY	aHR (95% CI)	PY	aHR (95% CI)	PY	aHR (95% CI)
Patients at risk	112,010		20,277		91,733	
Full EBCM combination	55,312	1.00	9,678	1.00	45,634	1.00
3-EBCM-based combinations						
ACEIs / ARBs + APAs + Beta-blockers	15,855	1.46 (1.33-1.60)	3,097	1.41 (1.20-1.65)	12,758	1.42 (1.26-1.59)
ACEIs / ARBs + APAs + Statins	9,623	0.99 (0.89-1.10)	1,321	0.99 (0.80-1.22)	8,302	0.99 (0.87-1.12)
ACEIs / ARBs + Beta-blockers + Statins	5,323	1.11 (0.98-1.25)	1,237	1.12 (0.92-1.38)	4,087	1.07 (0.92-1.24)
APAs + Beta-blockers + Statins	6,874	1.30 (1.17-1.43)	1,184	1.44 (1.21-1.71)	5,690	1.19 (1.05-1.35)
2-EBCM-based combinations						
ACEIs / ARBs + APAs	2,186	1.42 (1.22-1.66)	392	1.51 (1.16-1.98)	1,794	1.33 (1.10-1.61)
ACEIs / ARBs + Beta-blockers	1,157	1.39 (1.16-1.67)	338	1.38 (1.04-1.83)	819	1.38 (1.10-1.74)
ACEIs / ARBs + Statins	2,168	1.13 (0.94-1.36)	431	1.16 (0.85-1.58)	1,737	1.07 (0.85-1.34)
APAs + Beta-blockers	1,979	1.64 (1.43-1.88)	448	1.69 (1.34-2.12)	1,531	1.57 (1.31-1.87)
APAs + Statins	2,579	1.33 (1.14-1.55)	369	1.44 (1.10-1.89)	2,210	1.25 (1.04-1.51)
Beta-blockers + Statins	1,523	1.52 (1.28-1.81)	360	1.63 (1.24-2.14)	1,163	1.34 (1.05-1.70)
Single EBCM						
ACEIs / ARBs only	643	1.80 (1.39-2.32)	138	1.58 (1.01-2.47)	505	1.93 (1.46-2.56)
APAs only	839	1.96 (1.62-2.38)	161	1.77 (1.28-2.44)	678	2.12 (1.67-2.69)
Beta-blockers only	585	1.86 (1.52-2.26)	159	1.81 (1.33-2.47)	426	1.81 (1.40-2.34)
Statins only	3,039	1.69 (1.48-1.93)	509	1.82 (1.45-2.29)	2,530	1.58 (1.34-1.85)
No EBCM	2,324	2.27 (2.00-2.58)	455	2.30 (1.85-2.85)	1,869	2.24 (1.92-2.61)

ACEI, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; aHR, adjusted hazard ratio; APA, antiplatelet agent; ARB, angiotensin receptor blocker; CI, confidence interval; HF, heart failure; PY, person-year.

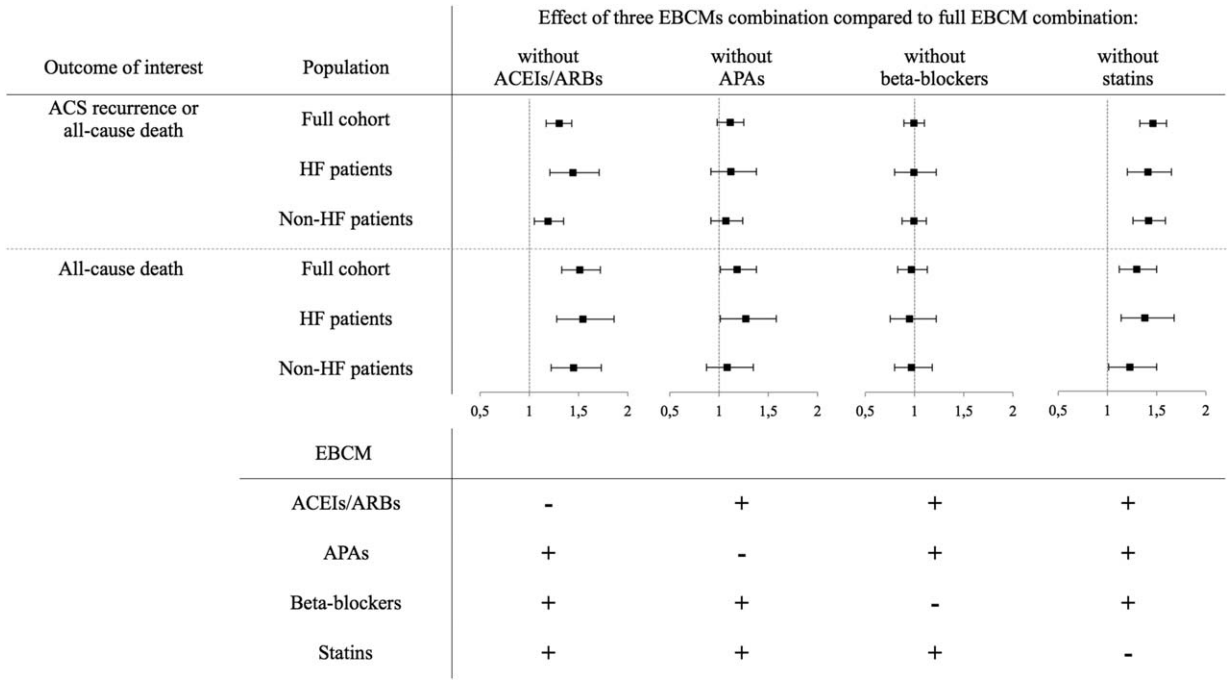

Figure 2 Effectiveness of 3-EBCM-based combinations compared to full EBCM combination according to several definitions of outcome and patient stratification. Estimates presented are adjusted hazard ratios of time-dependent Cox analyses with their 95% confidence intervals. ACEI, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; APA, antiplatelet agent; ARB, angiotensin receptor blocker; EBCM, evidence-based cardiovascular medications; HF, heart failure.

In addition to its size and representativeness of the general population, the database exhaustively records all reimbursed drugs (including all cardiovascular drugs identified here and low-dose aspirin) and all hospital stays (private and public). This made it possible to identify all events pertaining to the outcome of interest, providing that they led to hospitalization. Considering the nature of the health events of interest, this suggests that they were exhaustively identified, at least for the main outcome of interest.[26] Only ACS resulting in death before hospital admission could have gone unidentified, in which case they would have been considered for the all-cause death outcome. The detailed dates associated with these reimbursements and events leading to hospitalization allowed us to examine drug use in a time-varying manner with a daily assessment that took into account the theoretical time needed for each EBCM to be efficient. This is a particular strength of this study in addition to the fact that the drugs were studied as class combinations. The exhaustiveness of the information concerning outpatient drug reimbursement and hospitalization diagnoses allowed us to control for many potential confounders by using direct disease information or drug use as a proxy for these confounding factors and for the risk associated with the patient's background. However, owing to its focus on reimbursement, the electronic healthcare database does not include information on lifestyle, lab values, and other potential confounders such as body mass index. There may be proxies of these, such as chronic obstructive pulmonary disease for smoking, or diabetes for obesity, both associated with negative outcomes post-AMI.[27] While the adjustment performed in the analyses is likely to have allowed us to control for some of the potential biases due to unmeasured confounders, a residual effect cannot be excluded. Like all observational studies, this study cannot pretend to be as free of confounding as a well-conducted randomized controlled clinical trial. However, unlike the latter, it assesses the effect of a drug in a real-life setting, thus estimating its effectiveness and not only its intrinsic pharmacological efficacy. Since it deals with all existing situations, it also makes it possible to compare directly all EBCM drugs in combination among the diversity of patients treated for cardiovascular secondary prevention. This is a specific strength of the study, and its results are consistent with those of preexisting studies. Considering ACS as a whole, the full recommended EBCM combination appeared to be the most effective choice for secondary prevention, but the long-term effectiveness of beta-blockers in addition to the other EBCM was not demonstrated. Several pharmacoepidemiological studies have also evaluated the effectiveness of EBCMs in combination using a longitudinal definition of exposure.[8–10] However, they mainly considered the total number of drugs used in combination, and not the nature of the drugs constituting each particular combination, unlike in the present study. Moreover, those studies usually considered nonexposure for the reference category, a methodological choice that is open to criticism, as it is prone to exposing the study to a confounding and immeasurable time bias. We preferred instead to consider the 4-EBCM combination as the reference category for exposure to control for such biases.[16]

The long-term effectiveness of statins for secondary prevention in ACS patients was demonstrated in all analyses performed. The effect size found here for this drug class was consistent with that estimated in recent meta-analyses of clinical trials,[28–30] even

Table 3 Secondary analysis: Association between use of secondary prevention treatment during follow-up and occurrence of all-cause death, for the full cohort and stratified on the presence of heart failure at inclusion (Cox model)

	Full cohort		HF patients		Non-HF patients	
	PY	aHR (95% CI)	PY	aHR (95% CI)	PY	aHR (95% CI)
Patients at risk	122,131		22,127		100,003	
Full EBCM combination	60,880	1.00	10,670	1.00	50,209	1.00
3-EBCM-based combinations						
ACEIs / ARBs + APAs + Beta-blockers	16,576	1.30 (1.12-1.50)	3,259	1.38 (1.14-1.68)	13,317	1.23 (1.01-1.50)
ACEIs / ARBs + APAs + Statins	10,658	0.97 (0.83-1.13)	1,472	0.95 (0.75-1.22)	9,186	0.97 (0.80-1.18)
ACEIs / ARBs + Beta-blockers + Statins	5,742	1.18 (1.01-1.38)	1,323	1.27 (1.01-1.58)	4,419	1.08 (0.87-1.35)
APAs + Beta-blockers + Statins	7,722	1.51 (1.33-1.72)	1,360	1.54 (1.28-1.86)	6,362	1.45 (1.22-1.73)
2-EBCM-based combinations						
ACEIs / ARBs + APAs	2,341	1.24 (0.97-1.58)	413	1.34 (0.96-1.86)	1,929	1.24 (0.88-1.73)
ACEIs / ARBs + Beta-blockers	1,214	1.53 (1.20-1.96)	354	1.49 (1.07-2.08)	860	1.70 (1.23-2.34)
ACEIs / ARBs + Statins	2,341	1.48 (1.19-1.83)	459	1.44 (1.04-1.98)	1,881	1.48 (1.12-1.97)
APAs + Beta-blockers	2,117	2.00 (1.66-2.41)	483	2.03 (1.57-2.62)	1,634	1.98 (1.53-2.57)
APAs + Statins	2,859	1.55 (1.27-1.89)	404	1.47 (1.09-1.98)	2,455	1.57 (1.21-2.04)
Beta-blockers + Statins	1,677	1.80 (1.47-2.20)	396	1.73 (1.29-2.31)	1,280	1.70 (1.27-2.28)
Single EBCM						
ACEIs / ARBs only	676	1.68 (1.16-2.43)	145	1.73 (1.03-2.88)	531	1.77 (1.15-2.74)
APAs only	909	2.52 (1.95-3.25)	165	2.29 (1.60-3.27)	743	2.90 (2.13-3.96)
Beta-blockers only	618	2.23 (1.76-2.82)	169	2.30 (1.67-3.17)	449	2.37 (1.71-3.28)
Statins only	3,324	1.85 (1.56-2.20)	563	1.91 (1.49-2.46)	2,761	1.84 (1.48-2.30)
No EBCM	2,477	2.55 (2.15-3.01)	490	2.78 (2.20-3.52)	1,986	2.21 (1.73-2.82)

ACEI, angiotensin converting enzyme inhibitor; aHR, adjusted hazard ratio; APA, antiplatelet agent; ARB, angiotensin receptor blocker; CI, confidence interval; HF, heart failure; PY, person-year.

though they focused mainly on AMI. Similarly, the effectiveness found for ACEIs/ARBs is consistent with current knowledge, demonstrating a better effect in ACS patients with associated HF.[31–35] Our use of a large nationwide database provided substantial power; as in any study, however, the statistical significance of the tests performed should be seen in terms of the clinical meaning of the differences highlighted. Long-term use of beta-blockers and APAs appeared to have little effect on the reduction of ACS or all-cause death in patients without HF at inclusion. In contrast with the effects of beta-blockers, however, APAs were associated with a better long-term effect on all-cause death in the secondary analysis. This tends to demonstrate that use of APAs in real life could be effective on all-cause death but not on ACS recurrence. This apparent ineffectiveness might be due to the fact that many patients not using APAs were using anticoagulant agents (during follow-up, 40% of time unexposed to APAs were exposed to anticoagulants). Anticoagulant use can contraindicate the use of APAs and has a different mechanism of action on thrombosis; it could have an efficacy on ACS reduction equivalent to that of APAs. Consequently, users of APAs might be at equal risk for ACS recurrence, or have equal protection, as nonusers of APAs (including many anticoagulant users). As expected, however, the results concerning all-cause death suggest that the benefit–risk ratio of the latter is less favorable than that of APAs in the context of post-ACS treatment. As the aim of this study was to evaluate the long-term effectiveness of EBCM combinations, the methods and models we used were not adequate to allow assessing the benefit of dual antiplatelet therapy, which is not long-term recommended and could have a risk profile over follow-up very different from that of the other drugs studied in the combinations. If dual antiplatelet therapy assessment did not match our objective, it would, however, be of great importance, as observations of excessive durations for such treatments appears far from rare.[36] These results from a real-life setting in favor of a lack of clinically meaningful effectiveness of the long-term use of beta-blockers for post-ACS cardiovascular prevention are consistent with the results of other pharmacoepidemiological studies.[23–25] By comparison with these published data, it could be objected that the lack of effectiveness found for continuing beta-blockers in HF patients could result from methodological issues or residual confounding. If so, however, one could imagine that the situation resulting in confounding in that study

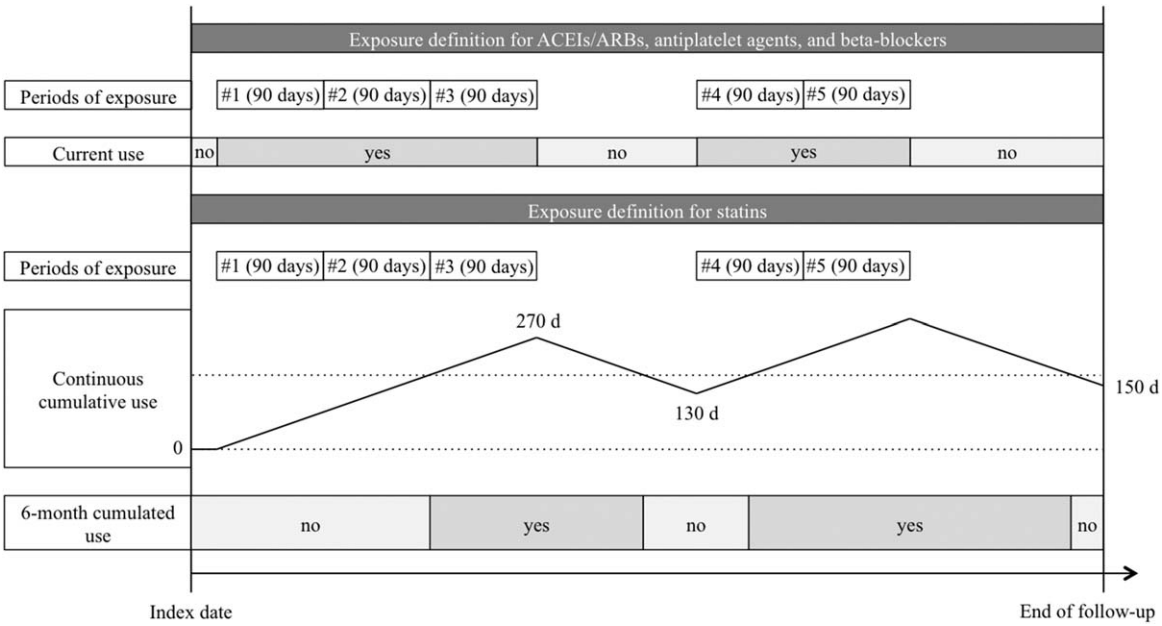

Figure 3 Definition of drug exposures. Exposure to angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), antiplatelet agents (APAs), and beta-blockers were defined as current use of the drugs corresponding to drug dispensation periods. Exposure to statins was defined as cumulative use of the drugs.

would specifically concern beta-blockers and not other drugs. Indeed, the results found for ACEIs/ARBs or statins are consistent with that of clinical trials, which lower the probability of confounding in the study, but even this cannot be fully ruled out. Finally, as randomized trials reevaluating the interest of beta-blockers in this indication are unlikely to be conducted, it seems important to consider such evidence, and the reconsideration of the place of beta-blockers in cardiovascular secondary prevention they advocate.

METHODS

Setting

This cohort study used data from the *Système National d'Informations Inter-Régimes de l'Assurance Maladie* (SNIIRAM) database.[37] This national healthcare insurance system database covers the entire French population and contains individual anonymous information on all outpatient reimbursed healthcare expenditures, registration status for a list of 30 specifically individualized chronic diseases, and hospital discharge data including diagnosis (coded with International Classification of Diseases 10th revision, ICD-10). In accordance with regulations, the study was authorized by the French commission for data privacy and by the French Institute on health data.

Study population

Patients were eligible for the study if they had been hospitalized for an incident ACS between 1st January 2010 and 31st December 2010, were aged 20 years and over at the date of ACS, were treated with the full EBCM combination in the 90 days following ACS, and were affiliated with the *general scheme* of the French health insurance system (the largest scheme, >50 million affiliates). Incident ACS was defined as first hospitalization for ACS (ICD-10 diagnosis codes I20.0, I21, or I24)[38] in the period, without identified history of ACS. Patients who died during this 90-day period were not included, early recurrence or death in the weeks following an initial ACS events being considered as depending essentially on the seriousness of the first event and only marginally on the effectiveness of the secondary prevention.[39]

Drug exposure

Drugs of interest were the four EBCMs recommended in secondary prevention of ACS: ACEIs or ARBs, APAs (aspirin and/or $P2Y_{12}$ inhibitor), beta-blockers, and statins. For each EBCM, the number of days of supply for each dispensing was defined as the number of tablets dispensed (assuming a treatment schedule of one tablet per day), to which a grace period equal to 10% of the number of tablets dispensed was added. Owing to the lack of data for drug exposure during hospitalization, all periods of hospital stay were considered as periods of exposure if the patient was in possession of drugs at the date of hospital admission.[16] Exposures were treated as time-dependent variables during follow-up, with different definitions between classes. Effects of ACEIs/ARBs, APAs, and beta-blockers were considered as almost immediate; exposure to these drugs was thus assessed according to the status for current use determined for these drugs on each particular day according to drug dispensing. Given the results of clinical trials, the clinical effects of statins were considered as delayed.[40,41] Exposure to statins was defined according to cumulative use of the drugs: the cumulative amount of use corresponded, at each day of follow-up, to the sum of days of supplies from the beginning of follow-up to that day minus the number of days without the drugs (**Figure 3**). Patients were considered as exposed to statins on a given day if they had a cumulative use of at least 6 months for the class on that day.[42] From this and the exposure status of patients for each day for ACEIs/ARBs, APAs, and beta-blockers, exposure to EBCMs was assessed on a daily basis over the follow-up, with a total of 16 categories of exposure to drug combinations. The combination associating the four EBCMs (referred to as the full EBCM combination) constituted the reference category for the different 3-EBCM-based combinations, 2-EBCM-based combinations, single EBCM exposures, and EBCM nonexposure.

Outcomes

The primary outcome of interest was the incidence of ACS recurrence or all-cause death. ACS recurrence was defined as for study population inclusion (ICD-10 diagnosis codes I20.0, I21, or I24).[38] The secondary outcome of interest was the incidence of all-cause death.

Statistical analysis

Patients included in the cohort were followed from the 90th day after the incident ACS date (index date) until the occurrence of the outcome of interest, the date removed from the database, or 31st December 2014, whichever came first. Effectiveness of EBCM combinations was analyzed by using the multivariable time-dependent Cox proportional hazards model.

To control for confounding, patient characteristics, comorbidities, and comedications considered as potential confounders were included in the models (see **Supplementary Table S1** for a description of selected covariates and corresponding identification codes). Owing to the potential impact of the presence of HF on the use of EBCM and on its effectiveness, especially for beta-blockers, models were stratified on the status of HF at inclusion.[4,7] Log-linearity, proportional hazard assumption, and collinearity were checked for all covariates in the models.

Statistical analyses were performed using SAS software (SAS Institute, v. 9.4, Cary, NC). Associations were estimated using aHRs and their corresponding 95% CI.

Additional Supporting Information may be found in the online version of this article.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

J.B., O.H.K, R.L., C.D.P., N.M., and A.P. wrote the article; J.B., O.H.K., N.M., and A.P. designed the research; J.B., O.H.K, R.L., C.D.P., N.M., and A.P. performed the research; J.B. analyzed the data.

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