

ORIGINAL REPORT

# Comparative effectiveness of recommended versus less intensive drug combinations in secondary prevention of acute coronary syndrome<sup>†</sup>

Julien Bezin<sup>1,2,3,4\*</sup> , Rolf H.H. Groenwold<sup>5,6</sup>, M. Sanni Ali<sup>5,6</sup>, Régis Lassalle<sup>4,7</sup>, Philip Robinson<sup>4,7</sup>, Anthonius de Boer<sup>5,6</sup>, Nicholas Moore<sup>1,2,3,4</sup> , Olaf H. Klungel<sup>5,6</sup> and Antoine Pariente<sup>1,2,3</sup>

<sup>1</sup>University of Bordeaux, U1219, Bordeaux, France

<sup>2</sup>Department of Clinical Pharmacology, University Hospital of Bordeaux, Bordeaux, France

<sup>3</sup>INSERM, U1219, Bordeaux Population Health Research Center, Pharmacoepidemiology Research Team, Bordeaux, France

<sup>4</sup>Bordeaux PharmacoEpi, INSERM CIC1401, Bordeaux, France

<sup>5</sup>Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

<sup>6</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>7</sup>ADERA, Pessac, France

## ABSTRACT

**Purpose** The secondary prevention treatment for acute coronary syndrome (ACS) is based on the combined use of drugs from four therapeutic classes (beta-blockers, antiplatelet agents, statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers). The objective of this study was to compare the long-term effectiveness of the recommended therapeutic combination with those of incomplete combinations in secondary prevention of ACS.

**Methods** This cohort study used data from a representative sample of the French national healthcare insurance system database. Patients hospitalised for an incident ACS between 2006 and 2011 and aged  $\geq 20$  years at the time of ACS were included in the study. Effectiveness in preventing the composite outcome ACS, transient ischemic attack, ischemic stroke or all-cause-death was estimated using time-fixed and time-dependent Cox proportional hazards models with different definitions of exposure (at inclusion or determined daily during follow-up) and adjustment for patient characteristics, co-morbidities and co-medications.

**Results** Of the 2874 patients included in the study, 33.9% were women; median age was 67 years (interquartile range: 56–77). The median duration of follow-up was 3.6 years (interquartile range: 2.2–5.3). Compared with the use of recommended combination, use of combination with three classes increased the risk of the composite outcome from 1.25 (95% confidence interval (95%CI), [1.07–1.47]) in the time-fixed model and from 1.40 (95%CI, [1.15–1.70]) or 1.42 (95%CI, [1.13–1.79]) in the time-dependent models.

**Conclusions** After ACS, the use of incomplete drugs combinations compared with the recommended four drugs combination was associated with a higher risk of cardiovascular morbidity and all-cause mortality. Copyright © 2017 John Wiley & Sons, Ltd.

**KEY WORDS**—acute coronary syndrome; secondary prevention; comparative effectiveness research; proportional hazards models

Received 21 September 2016; Revised 16 December 2016; Accepted 7 January 2017

## INTRODUCTION

Since 1996, guidelines recommend the combined use of drugs from four therapeutic classes: beta-blockers,

antiplatelet agents, statins and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for secondary prevention of acute coronary syndrome (ACS).<sup>1–8</sup> Adherence and persistence to these drugs are known to be often suboptimal at long term after the initial event, which could compromise the efficacy found in clinical trials.<sup>9–13</sup> For feasibility reasons, observational studies aiming to evaluate effectiveness of prevention define patient exposure status in a time-fixed way, either at the time of the initial event<sup>14–19</sup> or in the period preceding the outcome of interest.<sup>20–22</sup> These definitions of exposure could

\*Correspondence to: Julien Bezin, Service de Pharmacologie Médicale, Université de Bordeaux, CHU de Bordeaux, Bâtiment 1A, Zone Nord, Site Carreire, BP36, 146 rue Léo Saignat, F-33076 Bordeaux cedex, France. Email: julien.bezin@u-bordeaux.fr

<sup>†</sup>This study was presented as oral presentation in 2016 at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE) in Dublin, Ireland (Pharmacoepidemiol Drug Saf. 2016; 25 (S3):258) and at the Annual Meeting of French Society of Pharmacology and Therapeutics (SFPT) in Nancy, France (Fundam Clin Pharmacol. 2016; 30 (S1):13).

lead to misclassifications, and it is better to take into account changes over time of drug exposures and comorbidity status. Claims databases, which allow precisely identifying and dating drug dispensing and hospitalisation episodes, constitute a good data source for this type of drug evaluation in a real-life setting.

The objective of this study was to evaluate the influence of different methodologies and definitions of exposure on long-term effectiveness of incomplete drug combinations versus the recommended drug combination in secondary prevention after an ACS.

## METHODS

### *Setting*

This observational cohort study used data from the *Echantillon Généraliste de Bénéficiaires* (EGB) database.<sup>23–25</sup> This is a 1/97th representative sample of the population covered by the French national healthcare insurance system linked to the national hospital-discharge summary database Programme de Médicalisation des Systèmes d'Information (PMSI) and the national death registry, including beneficiaries without claims or hospitalisations. The EGB database contains individual anonymous information on (i) sex, year of birth and date of death (if applicable); (ii) outpatient dispensed healthcare expenditures such as drugs with date and code (but not drugs used in hospital); (iii) hospital discharge summaries from PMSI, with International Classification of Diseases 10th revision (ICD-10) codes for main, related and associated diagnosis, the date and duration of hospitalisation and medical procedures; and (iv) registration, with date and ICD-10 code, for a list of 30 long-term diseases (LTD) including coronary disease, and allowing the patient to receive full reimbursement (100%) for expenditure related to the LTD.

### *Study population*

Patients were eligible for the study if they had been hospitalised for an incident ACS between 1 January 2006 and 31 December 2011, aged 20 years and over at the time of ACS, affiliated to the general French health insurance system and present in the database at least 1 year before the date of ACS. Incident ACS was defined as the first hospitalisation for ACS (ICD-10 codes I20.0, I21 or I24 in main diagnosis) in the period, without identified history of ACS (no previous LTD registration for ACS and no previous hospitalisation with main, associated or related diagnosis of ACS).<sup>26</sup> Patients without any dispensing of at least one of the four recommended drug classes in

the first 90 days (i.e. 3 months) following ACS occurrence were not included in the cohort as it probably correspond to misdiagnosis or to patients for which drugs deliveries are not available in the database. Similarly, patients who died during this period were not included as early events relate more to the first event than to the effectiveness of the secondary prevention.

### *Outcome*

All patients included in the cohort were followed from the 90th day after the incident ACS occurrence (index date) until the incidence of a major adverse cardiac event (MACE), death, date removed from the database or 31 December 2013, whichever came first. MACE was defined as hospitalisation for ACS (main diagnosis: I200, I21 or I24 ICD-10 codes), transient ischemic attack (main diagnosis: G45 code, G454 excluded) or ischemic stroke (main diagnosis: I63 code, or main diagnosis: G46 with I63 in associated diagnosis). The outcome was incidence of MACE or all-cause-death, whichever came first.

### *Drug exposure*

Drugs of interest were the following four therapeutic classes: beta-blockers (ATC code: C07), antiplatelet agents (B01AC), statins (C10AA, C10BA and C10BX), and ACEIs or ARBs (C09A, C09B, C09C and C09D). For each class, the number of days of supply for each dispensation 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. Overlapping days supplied with successive deliveries for the same drug (same ATC code) were added to the number of days of supply. Because of a potential lack of data during hospitalisation considering drug exposure, all periods of hospital stay were considered as exposed if the patient was in possession of drugs at the date of hospital admission.<sup>27</sup> Exposure to drug combinations was defined according to the number of therapeutic classes used: combination associating the four therapeutic classes (reference), combination with only three of the four classes, combination with only two of the four classes, combination with only one of the four classes and none of the four classes.

### *Potential confounders*

Several covariates were defined to adjust for confounding in multivariable analyses. (1) General characteristics: age at initial ACS, sex, number of different drugs

used in the 6-month period before initial ACS, number of medical consultations in the 6-month period before initial ACS and patient status of full healthcare coverage for low-income status during follow-up. (ii) Characteristics of the initial ACS: diagnosis (according to ICD-10: acute myocardial infarction, unstable angina or other ischaemic heart diseases), duration of hospitalisation stay, medical procedure (percutaneous coronary intervention or coronary artery bypass grafting) performed during hospitalisation, use of therapeutic classes of interest in the 6-month period before initial ACS and number of hospitalisation for MACE in the 3-month period after initial ACS. (3) Co-morbidities: asthma (hospitalisation), bundle-branch block (hospitalisation), cancer (hospitalisation or LTD registration), cardiac arrhythmia (hospitalisation or LTD registration for cardiac arrhythmia or use of anti-arrhythmic drugs), cardiac failure (hospitalisation or LTD registration), cerebral haemorrhage (hospitalisation), chronic obstructive pulmonary disease (hospitalisation), diabetes (hospitalisation or LTD registration for diabetes or use of anti-diabetic drugs), gastrointestinal haemorrhage (hospitalisation), hepatic failure (hospitalisation), hypertension (hospitalisation), peripheral artery disease (hospitalisation), use of anticoagulant drugs, calcium channel blockers, diuretics, nitrates, other anti-hypertensive drugs (central antihypertensive drugs, alpha-adrenoreceptor antagonists, dihydralazine and minoxidil) and other lipid-lowering agents (fibrates, bile acid sequestrants, ezetimib, tiadenol and omega-3).

### Analytic methods

Statistical analyses were performed using SAS® software (version 9.4, SAS Institute, NC, USA). Standard descriptive statistics as appropriate to the nature of the data were used to describe patient characteristics at baseline (i.e. at index date), patient exposure in the 3-month period following initial ACS and patient exposure during follow-up.

Effectiveness of combinations of therapeutic classes of interest and the effectiveness of the four therapeutic

classes of interest individually were assessed regarding the occurrence of MACE or all-cause-death during follow-up. These effectiveness analyses were performed using Cox proportional hazards models under four scenarios. In the first scenario, exposures were defined according to drug dispensing in the 3-month period following initial ACS and then considered fixed (intention-to-treat; Figure 1). Multivariable analyses for scenario 1 were adjusted for time-fixed confounders at baseline. For the second, third and fourth scenarios, drug-by-day matrices were created for each patient during follow-up (per-protocol; Figure 1), that is, for each day of follow-up, patients were classified in each exposure groups according to their exposures on the day considered.<sup>28</sup> In the second scenario, exposure to each therapeutic class and combinations were defined as current use; patients were classified as exposed if they were in possession of the drug on the day considered (Figure 2). In the third and fourth scenarios, based on results of clinical trials,<sup>29,30</sup> beta-blockers and statins were considered as having delayed clinical effects, opposed to anti-platelet agents and ACEIs/ARBs considered as having rapid clinical effects. Exposure to beta-blockers and statins was defined as cumulative use, days in possession of drugs were added and days without drugs were subtracted from index date until the end of follow-up (Figure 2). This cumulative exposure was considered as a dichotomous variable using a threshold of 6-month cumulated use to be exposed in order to constitute combinations of interest (scenario 3) and also as a continuous variable (scenario 4). Similarly to scenario 2, exposures to anti-platelet agents and to ACEIs/ARBs were defined according to current use. Multivariable analyses for scenarios 2, 3 and 4 were adjusted for time-fixed confounders measured at baseline and time-dependent confounders measured during follow-up.

Log-linearity, proportional hazard assumption and co-linearity were checked for all covariates in the models built for each scenario. Interactions between the individual therapeutic classes studied were also



Figure 1. Definition of periods of exposure. ACS, acute coronary syndrome

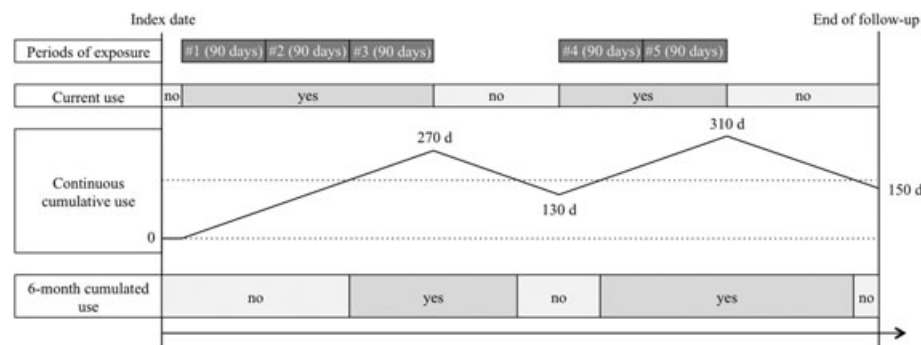


Figure 2. Definition of drugs exposures for scenarios 2, 3 and 4

assessed in models estimating effectiveness of the four therapeutic classes of interest individually.

*Regulatory aspects*

In accordance with regulations in place at the time of the study, the National Institute of Health and Medical Research (*Institut National de la Santé et de la Recherche Médicale*) was informed of the study to be performed using the EGB database. There was no other requirement for ethical approval of this study.

RESULTS

Overall, 2874 patients who had experienced an incident ACS between 1 January 2006 and 31 December 2011 were included in the study (Figure 3). At the time of ACS, median patient age was 67 years (interquartile range, IQR: 56–77), 33.9% were women and 52.8% had experienced an acute myocardial infarction (Table 1). The median duration of follow-up was 3.6 years (IQR: 2.2–5.3), and the total of follow-up was 10,676 person-years. There were 417 MACE

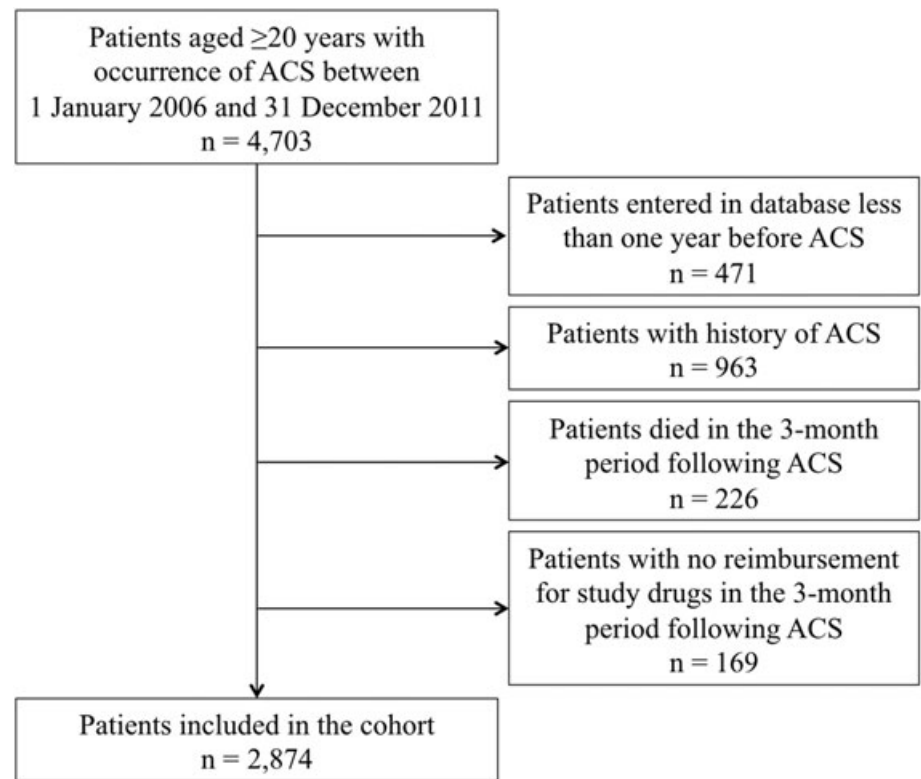


Figure 3. Flow chart of the study patient identification process. ACS, acute coronary syndrome



Table 1. Patient characteristics at baseline

	Cohort <i>n</i> = 2874
Age at ACS – year, median [IQR]	67 [56–77]
Sex – female, <i>n</i> (%)	973 (33.9)
Diagnosis of initial ACS, <i>n</i> (%)	
Acute myocardial infarction	1517 (52.8)
Unstable angina	1193 (41.5)
Other acute ischaemic heart diseases	164 (5.7)
Procedure (PCI/CABG) during initial ACS hospitalisation, <i>n</i> (%)	1525 (53.1)
Duration of initial ACS hospitalisation – day, median [IQR]	5 [3–8]
Co-morbidities and co-medications in the year before initial ACS, <i>n</i> (%)	
Asthma	5 (0.2)
Bundle-branch block	10 (0.3)
Cancer	333 (11.6)
Cardiac arrhythmia	356 (12.4)
Cardiac failure	202 (7.0)
Cerebral haemorrhage	1 (0.0)
Chronic obstructive pulmonary disease	7 (0.2)
Diabetes	739 (25.7)
Gastrointestinal haemorrhage	11 (0.4)
Hepatic failure	4 (0.1)
Hypertension	12 (0.4)
Peripheral artery disease	43 (1.5)
Use of anticoagulant	520 (18.1)
Use of calcium channel blockers	944 (32.8)
Use of diuretics	941 (32.7)
Use of nitrate	1434 (49.9)
Use of other antihypertensive drugs	225 (7.8)
Use of other lipid-lowering agents	516 (18.0)
Full healthcare coverage for low-income status, <i>n</i> (%)	165 (5.7)
Number of different drugs in the 6 months before initial ACS, median [IQR]	9 [5–15]
Number of consultations in the 6 months before initial ACS, median [IQR]	4 [2–7]
Use of therapeutic classes of interest in the 6 months before initial ACS, <i>n</i> (%)	
Beta-blockers	787 (27.4)
Antiplatelet agents	889 (30.9)
Statins	897 (31.2)
ACEI or ARB	1209 (42.1)
Hospitalisation for MACE in the 3 months after initial ACS, <i>n</i> (%)	330 (11.5)

ACEI, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; IQR, interquartile range; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention.

and 527 all-cause-deaths during follow-up, resulting in 844 MACE or all-cause-death events (mean annual incidence of 7.9%).

In scenario 1 (intention-to-treat), 58.4% of patients were exposed to the recommended combination of four classes, 28.1% had combination with three classes, 9.7% had combinations with two classes and 3.7% had only one class. In multivariate time-fixed analysis, exposure to incomplete combination in the three months following ACS, regardless of the number of therapeutic classes used, was statistically associated with a higher risk of MACE or all-cause-death compared with the

exposure to the complete combination with four classes. This higher risk increased according to the number of therapeutic classes not used: 1.25 (95%CI, [1.07–1.47]) for the combination of three classes, 1.54 (95%CI, [1.22–1.94]) for the combination of two classes and 1.76 (95%CI, [1.25–2.48]) for one class (Table 2). Concerning each therapeutic class independently, 83.3% of patients had beta-blockers during the 3 months following ACS, 94.3% had antiplatelet agents, 87.4% had statins and 78.3% had ACEIs/ARBs. In multivariate time-fixed analysis, an interaction was found between the use in the 3 months following ACS of beta-blockers and antiplatelet agents; occurrence of events was 1.38 times higher (95%CI, [0.82–2.34]) for patients with beta-blockers and antiplatelet agents than for patients without these two drugs. Use of statins compared with non-use (HR, 0.61; 95%CI, [0.49–0.74]) and use of ACEIs/ARBs compared with non-use (HR, 0.90; 95%CI, [0.74–1.10]) were both associated to a lower risk of MACE or all-cause-death (Table 3).

In scenario 2 (per-protocol), which considered exposure as current use during follow-up, exposed-time to the combination of four classes was 38.7% of follow-up, 31.2% for the combination of three classes, 14.1% for the combination of two classes, 8.1% for the combination of one class and 8.0% for none of the four classes. Multivariate time-dependant analysis showed higher associations between use of incomplete combinations and occurrence of MACE or all-cause-death, even more so than scenario 1 (Table 2). Concerning each therapeutic class independently, exposed-time to beta-blockers was 66.1% of follow-up, those to antiplatelet agents was 78.4%, those to statins was 74.2% and those to ACEIs/ARBs was 65.8%. Multivariate time-dependant analysis showed a lower risk of MACE or all-cause-death with current use of statins (HR, 0.63; 95%CI, [0.52–0.75]) and with current use of ACEIs/ARBs (HR, 0.71; 95%CI, [0.60–0.85]). Current use of beta-blockers and current use of antiplatelet agents were not significantly associated to a lower risk of events (Table 3).

In scenario 3 (per-protocol), which considered exposure to beta-blockers and statins as 6-month cumulated use during follow-up, exposed-times to the combination of four classes (33.1%) and to the three classes (28.0%) were lower compared with scenario 2 (38.7% and 31.2%, respectively). In multivariate time-dependant analysis, point estimates of the association between use of combinations of three, or two classes and occurrence of MACE or all-cause-death were slightly higher in scenario 3 compared with scenario 2 (Table 2). Concerning each therapeutic class independently,

Table 2. Association between use of secondary prevention drug combinations and occurrence of MACE or all-cause death (Cox models)

			Adjusted HR <sup>a</sup> [95% CI]
Scenario 1: time-fixed model, exposure defined in the 3-month period following incident ACS			
Patients at risk	2874 patients		
Combination with 4 classes	1679 patients	1	
Combination with 3 classes	809 patients	1.25	[1.07–1.47]
Combination with 2 classes	280 patients	1.54	[1.22–1.94]
Only 1 class	106 patients	1.76	[1.25–2.48]
0 class	—	—	—
Scenario 2: time-dependent model, exposure daily defined during follow-up as current use			
Patients at risk	10,676 patient-years		
Combination with 4 classes	4128 patient-years	1	
Combination with 3 classes	3331 patient-years	1.40	[1.15–1.70]
Combination with 2 classes	1505 patient-years	1.73	[1.37–2.20]
Only 1 class	862 patient-years	2.53	[1.95–3.27]
0 class	850 patient-years	2.80	[2.16–3.62]
Scenario 3: time-dependent model, exposure daily defined during follow-up as current use for antiplatelet agents and ACEI/ARB and as 6-month cumulated use for beta-blockers and statins			
Patients at risk	10,676 patient-years		
Combination with 4 classes	3536 patient-years	1	
Combination with 3 classes	2990 patient-years	1.42	[1.13–1.79]
Combination with 2 classes	2376 patient-years	2.10	[1.65–2.66]
Only 1 class	1144 patient-years	2.40	[1.80–3.20]
0 class	630 patient-years	3.39	[2.49–4.61]

ACEI, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin receptor blockers; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events.

<sup>a</sup>Adjusted on potential confounders defined at baseline or in the year before initial ACS for scenario 1 and during follow-up for scenarios 2 and 3.

Table 3. Association between use of individual secondary prevention drug classes and occurrence of MACE or all-cause death (Cox models)

			Adjusted HR <sup>a</sup> [95% CI]
Scenario 1 <sup>b</sup> : time-fixed model, exposure defined in the 3-month period following incident ACS			
Patients at risk	2874 patients		
Beta-blockers and antiplatelet agents			
Non-use of beta-blockers and antiplatelet agents	60 patients	1	
Use of beta-blockers and non-use of antiplatelet agents	103 patients	1.39	[0.76–2.54]
Non-use of beta-blockers and use of antiplatelet agents	420 patients	1.87	[1.10–3.18]
Use of beta-blockers and antiplatelet agents	2291 patients	1.38	[0.82–2.34]
Statins – use versus non-use	2512 patients	0.61	[0.49–0.74]
ACEI/ARB – use versus non-use	2249 patients	0.90	[0.74–1.10]
Scenario 2: time-dependant model, exposure daily defined during follow-up			
Patients at risk	10,676 patient-years		
Beta-blockers – current use versus no current use	7053 patient-years	0.93	[0.78–1.10]
Antiplatelet agents – current use versus no current use	8374 patient-years	0.85	[0.70–1.03]
Statins – current use versus no current use	7922 patient-years	0.63	[0.52–0.75]
ACEI/ARB – current use versus no current use	7027 patient-years	0.71	[0.60–0.85]
Scenario 3: time-dependant model, exposure daily defined during follow-up			
Patients at risk	10,676 patient-years		
Beta-blockers – 6-month cumulated use versus no 6-month cumulated use	6270 patient-years	0.90	[0.74–1.09]
Antiplatelet agents – current use versus no current use	8374 patient-years	0.76	[0.63–0.91]
Statins – 6-month cumulated use versus no 6-month cumulated use	7358 patient-years	0.71	[0.57–0.87]
ACEI/ARB – current use versus no current use	7027 patient-years	0.67	[0.57–0.80]
Scenario 4: time-dependant model, exposure daily defined during follow-up			
Patients at risk	10,676 patient-years		
Beta-blockers – continuous cumulative use (per year of use)	—	0.95	[0.88–1.03]
Antiplatelet agents – current use versus no current use	8374 patient-years	0.76	[0.63–0.92]
Statins – continuous cumulative use (per year of use)	—	0.88	[0.81–0.96]
ACEI/ARB – current use versus no current use	7027 patient-years	0.67	[0.57–0.80]

ACEI, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin receptor blockers; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events.

<sup>a</sup>Adjusted on potential confounders defined at baseline or in the year before initial ACS for scenario 1 and during follow-up for scenarios 2 and 3.

<sup>b</sup>Significant interaction between beta-blockers and antiplatelet agents.

exposed-time to beta-blockers was reduced from 66.1% in scenario 2 to 58.7% and exposed-time to statins from 74.2% in scenario 2 to 68.9%. Multivariate time-dependent analyses showed a lower risk of MACE or all-cause-death with current use of antiplatelet agents (HR, 0.76; 95%CI, [0.63–0.91]), with 6-month cumulated use of statins (HR, 0.71; 95%CI, [0.57–0.87]) and with current use of ACEIs/ARBs compared with non-use (HR, 0.67; 95%CI, [0.57–0.80]; Table 3).

In scenario 4 (per-protocol), the results of multivariate time-dependent analyses with definition of exposures to beta-blockers and statins as a continuous cumulative use variable were similar to scenario 3 (Table 3).

## DISCUSSION

After occurrence of ACS, the use of incomplete drug combinations compared with the recommended four drugs combination was associated with a higher risk of the composite outcome of MACE or all-cause-death over a long-term follow-up. However, when considering individually each recommended drug class, we did not find evidence of a long-term benefit of beta-blocker use independently of the other drug classes.

Whatever the number of drugs used, incomplete drug combinations in secondary prevention of ACS were significantly associated with a higher risk of MACE or all-cause-death in the long term compared with the recommended four drugs combination. This result was found consistent over all analyses performed. Indeed, in this study, as recommended in pharmacoepidemiology practice guidelines,<sup>31–33</sup> we considered different scenarios to build statistical models that allow estimating the effect of the recommended combination in real life. In all these scenarios, which considered either exposure from a pragmatic approach (time-fixed models, intention-to-treat like) either by taking into account the exact current exposure and the time-period needed for it to be efficient (time-dependent models, per-protocol like), results were similar: the lower the number of recommended drugs that is used, the higher the risk of MACE or death. Causes of non-exposure to drug(s) of interest are multiple such as drug discontinuation because of an adverse effect, inappropriate to prescribe a drug because of a contra-indication or patient initiated non-adherence or non-persistence.<sup>34</sup> It is important to identify those patients that are non-adherent or discontinuing medication for non-medical reasons to try to improve the compliance of the recommended regimen. Similar trends were found in other studies in which the impact of incomplete drug combinations on the recurrence of CV events or all-cause mortality in

secondary prevention of ACS was evaluated. In these studies, methods generally adopted a time-fixed approach (intention-to-treat like), as in scenario 1.<sup>14–22</sup> Our study confirms the results of clinical trials evaluating the individual effectiveness of antiplatelet agents, statins and ACEIs/ARBs.<sup>5–8</sup> Moreover, the cumulative effectiveness of statin was confirmed in time-dependent scenarios, which consider a definition of exposure for statin by taking into account the theoretical time required for the establishment of the effectiveness (scenario 3) or by a cumulative use (scenario 4). However for beta-blockers, independently of the other therapeutic classes, no effect was found in the risk of MACE or death over this study with a long-term follow-up. This discrepancy could relate to the differences (including global management) between the populations currently treated post-ACS and the populations explored more than three decades ago in trials of beta-blockers efficacy. Our results concerning beta-blockers are consistent with those of recent studies.<sup>17,35</sup> These results highlight the need to reconsider the place of beta-blockers in the long-term management of ACS.

In the context of chronic exposure and long follow-up, this study underlines that using a time-fixed definition for exposure assessment is likely to impact significantly the estimates if adherence or persistence were found suboptimal. If this impact did not lead to reverse associations for the effect of combination, it led to underestimate the associations found. Compared with time-fixed definition of exposure, results of models evaluating the impact of non-use of the recommended combination was much higher when exposure was defined as time-dependent and differences in estimates between each category of combinations were more pronounced. In addition, our results showed a higher risk of MACE or death as soon as a therapeutic class was missing, which is not apparent in other observational studies. Such results could have been expected as adherence and persistence in post-ACS are known to be suboptimal in secondary cardiovascular prevention.<sup>9–13</sup>

The main strength of this study is that we have explored different designs and definitions for classification of exposures.<sup>31–33</sup> Besides the classic time-dependent definition of exposure as current use at the time of event (scenario 2), scenario 3 took into account the theoretical time required for the establishment of the effectiveness of beta-blockers and statins, and scenario 4 allowed estimating the impact of cumulative use for beta-blockers and statins. The database used presents important strengths: it is representative of more than three-quarters of the French population corresponding to the main health insurance regimen in France,<sup>24,25,36</sup> and it includes all reimbursed

outpatient drugs, as is the case for all cardiovascular drugs of interest in this work. However, the database used for this study does not allow identifying drugs dispensed during hospitalisation. To deal with this lack of information, patients were considered exposed for all time-periods of hospital stay in our study for the drugs they were in possession at the date of hospital admission.<sup>27</sup> Another strength of this study is that it used an ACS definition that has been previously validated (predictive positive value of 84.2%; 95%CI, [72.1–92.5]).<sup>26</sup> Finally, the main limitation of this type of database is the lack of certain risk factors and potential confounders such as smoking and overweight. The potential effect of this unmeasured confounding should have been minimised in our study by the time-dependent multivariate adjustment for co-morbidities and co-medications. Amongst these unmeasured confounders, the lack of observance of lifestyle recommendations could be of importance. However, under the hypothesis that patients not respecting these recommendations should also constitute those less likely to be adherent to their treatments, time-dependent models taking into account adherence for treatment evaluation could have indirectly and partially adjusted for such unmeasured confounders.

In conclusion, the use of incomplete drug combinations compared with the recommended four drugs combination was associated with a higher risk of MACE or all-cause-death in the long-term after occurrence of ACS. Time-dependent definitions of exposure seem to be the most precise way for comparative effectiveness in this context. This study moreover advocates for the conduct of studies specifically designed to evaluate the place of beta-blockers amongst the other recommended drugs in post-ACS treatment in real-life setting.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## KEY POINTS

- Time-dependent definitions of exposure seem to be the most precise way for comparative effectiveness in the context of cardiovascular secondary prevention evaluation.
- Use of incomplete drugs combinations compared with the recommended four drugs combination in secondary prevention of ACS was associated with a higher risk of cardiovascular morbidity and all-cause mortality.

## ACKNOWLEDGEMENTS

This project has received support from the French government managed by the National Research Agency under the Investments for the Future scheme (grant number ANR-10-IDEX-03-02) and a research grant from an association for the development of research with universities in Aquitaine (ADERA).

## REFERENCES

1. Acute myocardial infarction: pre-hospital and in-hospital management. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 1996; **17**: 43–63.
2. Ryan TJ, Anderson JL, Antman EM, *et al.* ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1996; **28**: 1328–1428.
3. Braunwald E, Antman EM, Beasley JW, *et al.* ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on the management of patients with unstable angina). *Circulation* 2000; **102**: 1193–1209.
4. Bertrand ME, Simoons ML, Fox KA, *et al.* Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation; recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J* 2000; **21**: 1406–1432. doi:10.1053/ehuj.2000.2301.
5. Steg PG, James SK, Atar D, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33**: 2569–2619. doi:10.1093/eurheartj/ehs215.
6. Roffi M, Patrono C, Collet JP, *et al.* 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European society of cardiology (ESC). *Eur Heart J* 2016; **37**: 267–315. doi:10.1093/eurheartj/ehv320.
7. Levine GN, Bates ER, Blankenship JC, *et al.* 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the society for cardiovascular angiography and interventions. *Circulation* 2015. doi:10.1161/CIR.0000000000000336.
8. Amsterdam EA, Wenger NK, Brindis RG, *et al.* 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation* 2014; **130**: 2354–2394. doi:10.1161/CIR.0000000000000133.
9. Bezin J, Pariente A, Lassalle R, *et al.* Use of the recommended drug combination for secondary prevention after a first occurrence of acute coronary syndrome in France. *Eur J Clin Pharmacol* 2014; **70**: 429–436. doi:10.1007/s00228-013-1614-5.
10. Bourdes V, Ferrieres J, Amar J, *et al.* Prediction of persistence of combined evidence-based cardiovascular medications in patients with acute coronary syndrome after hospital discharge using neural networks. *Med Biol Eng Comput* 2011; **49**: 947–955. doi:10.1007/s11517-011-0785-4.
11. Gislason GH, Rasmussen JN, Abildstrom SZ, *et al.* Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J* 2006; **27**: 1153–1158. doi:10.1093/eurheartj/ehi705.
12. Kotseva K, Wood D, De Bacquer D, *et al.* EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2015. doi:10.1177/2047487315569401.
13. Ringback Weitof G, Ericsson O, Lofroth E, *et al.* Equal access to treatment? Population-based follow-up of drugs dispensed to patients after acute myocardial infarction in Sweden. *Eur J Clin Pharmacol* 2008; **64**: 417–424. doi:10.1007/s00228-007-0425-y.
14. Allen LA, O'Donnell CJ, Giugliano RP, *et al.* Care concordant with guidelines predicts decreased long-term mortality in patients with unstable angina pectoris and non-ST-elevation myocardial infarction. *Am J Cardiol* 2004; **93**: 1218–1222. doi:10.1016/j.amjcard.2004.01.063.



15. Briffa T, Hickling S, Knuiman M, *et al.* Long term survival after evidence based treatment of acute myocardial infarction and revascularisation: follow-up of population based Perth MONICA cohort, 1984–2005. *BMJ* 2009; **338**: b36. doi:10.1136/bmj.b36.
16. Gunnell AS, Einarsdottir K, Sanfilippo F, *et al.* Improved long-term survival in patients on combination therapies following an incident acute myocardial infarction: a longitudinal population-based study. *Heart* 2013; **99**: 1353–1358. doi:10.1136/heartjnl-2013-304348.
17. Hamood H, Hamood R, Green MS, *et al.* Effect of adherence to evidence-based therapy after acute myocardial infarction on all-cause mortality. *Pharmacoepidemiol Drug Saf* 2015; **24**: 1093–1104. doi:10.1002/pds.3840.
18. Kumbhani DJ, Steg PG, Cannon CP, *et al.* Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. *Am J Med* 2013; **126**: 693–700. doi:10.1016/j.amjmed.2013.01.033.e1
19. Tuppin P, Neumann A, Danchin N, *et al.* Evidence-based pharmacotherapy after myocardial infarction in France: adherence-associated factors and relationship with 30-month mortality and rehospitalization. *Arch Cardiovasc Dis* 2010; **103**: 363–375. doi:10.1016/j.acvd.2010.05.003.
20. Kirchmayer U, Di Martino M, Agabiti N, *et al.* Effect of evidence-based drug therapy on long-term outcomes in patients discharged after myocardial infarction: a nested case-control study in Italy. *Pharmacoepidemiol Drug Saf* 2013; **22**: 649–657. doi:10.1002/pds.3430.
21. Kuepper-Nybelen J, Hellmich M, Abbas S, *et al.* Association of long-term adherence to evidence-based combination drug therapy after acute myocardial infarction with all-cause mortality. A prospective cohort study based on claims data. *Eur J Clin Pharmacol* 2012; **68**: 1451–1460. doi:10.1007/s00228-012-1274-x.
22. van der Elst ME, Bouvy ML, de Blaeij CJ, *et al.* Effect of drug combinations on admission for recurrent myocardial infarction. *Heart* 2007; **93**: 1226–1230. doi:10.1136/hrt.2006.098053.
23. Moulis G, Lapeyre-Mestre M, Palmaro A, *et al.* French health insurance databases: what interest for medical research? *La Revue de medecine interne/fondée par la Société nationale française de medecine interne* 2015; **36**: 411–417. doi:10.1016/j.revmed.2014.11.009.
24. De Roquefeuil LSA, Neumann A, Merlière Y. The *Echantillon généraliste de bénéficiaires*: representativeness, scope and limits. *Pratiques et Organisation des Soins* volume 2009; **40**: 213–223.
25. Tuppin P, de Roquefeuil L, Weill A, *et al.* French national health insurance information system and the permanent beneficiaries sample. *Rev Epidemiol Sante Publique* 2010; **58**: 286–290. doi:10.1016/j.respe.2010.04.005.
26. Bezin J, Girodet PO, Rambelomanana S, *et al.* Choice of ICD-10 codes for the identification of acute coronary syndrome in the French hospitalization database. *Fundam Clin Pharmacol* 2015; **29**: 586–591. doi:10.1111/fcp.12143.
27. Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. *Am J Epidemiol* 2008; **168**: 329–335. doi:10.1093/aje/kwn135.
28. Levy AR, Tamblyn RM, Abrahamowicz M, *et al.* Use of time-dependent measures to estimate benefits of beta-blockers after myocardial infarction. *Pharmacoepidemiol Drug Saf* 2004; **13**: 623–631. doi:10.1002/pds.944.
29. Hultén E, Jackson JL, Douglas K, *et al.* The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; **166**: 1814–1821. doi:10.1001/archinte.166.17.1814.
30. Freemantle N, Cleland J, Young P, *et al.* Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; **318**: 1730–1737.
31. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology (Revision 4). EMA/95098/2010. Available at [http://www.encepp.eu/standards\\_and\\_guidances](http://www.encepp.eu/standards_and_guidances).
32. Stricker BH, Stijnen T. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. *Eur J Epidemiol* 2010; **25**: 245–251. doi:10.1007/s10654-010-9451-7.
33. ISPE. Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Saf* 2008; **17**: 200–208. doi:10.1002/pds.1471.
34. Salvo F, Bezin J, Bosco-Levy P, *et al.* Pharmacological treatments of cardiovascular diseases: Evidence from real-life studies. *Pharmacol Res* 2016. doi:10.1016/j.phrs.2016.08.006.
35. Bangalore S, Steg G, Deedwania P, *et al.* Beta-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 2012; **308**: 1340–1349. doi:10.1001/jama.2012.12559.
36. Martin-Latry K, Begaud B. Pharmacoepidemiological research using French reimbursement databases: yes we can! *Pharmacoepidemiol Drug Saf* 2010; **19**: 256–265. doi:10.1002/pds.1912.