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## THERAPIES

### HEADING: PHARMACOEPIDEMOLOGY

#### Six-year survival study after myocardial infarction: the EOLE prospective cohort study

Long-term survival after MI

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## Summary

*Background.*- Studies of survival after myocardial infarction (MI) are often based on intention to treat analyses of controlled trials. *Objectives.*- Describe long-term survival after MI in France. *Methods.*- Six-year cohort study of patients recruited within 3 months after MI. Primary outcome was all-cause death. Vital status was verified in the national death registry. Analysis used Cox models with time-dependent variables and propensity scores. *Results.*- Five thousand five hundred and twenty-seven (5527) subjects were included, 62.1±13 years old, 77.6% male, 9.6% smokers, 16.7% diabetic, 13.3% with previous MI. Up to 99% of patients were initially prescribed secondary prevention drugs (aspirin and/or other antiplatelet agents, beta-blockers, statins or other lipid-lowering agents, angiotensin converting enzyme inhibitors or angiotensin receptor blockers); 73% had all four classes. Overall 6-year mortality was 13.1% [95% confidence interval 12.3 to 14.0%], 2.34 per hundred patient-years (% PY); 49% returned all or all but one of the possible questionnaires (compliant [C]), 50.8% did not (non-compliant [NC]). The main predictors for death were non-compliance with study protocol (death rates NC 2.98 % PY, C 1.69 %PY, hazard ratio (HR) 3.13 [2.63-3.57]); increasing age at inclusion (HR up to 15.7 [10.7-23.2] for age ≥80); diabetes (1.39 [1.17-1.65]); smoking at inclusion (1.76 [1.27-2.44]), previous MI (1.46 [1.22-1.75]). Beta-blockers (0.79 [0.64-0.96]), statins (0.68 [0.51-0.90]), and enrolment in physical rehabilitation programs (0.74 [0.62-0.89]) were associated with a lower death rate. *Conclusion.*- Association of mortality with non-compliance to study protocol probably indicates general non-compliance with prevention. Analyses of treatment effects were hindered by paucity of events and of unexposed patients.

## KEYWORDS

Myocardial infarction; Long-term outcomes; Cohort study; Pharmacoepidemiology; Mortality

## Abbreviations

ACEI: angiotensin converting enzyme inhibitors

ARB: angiotensin receptor blockers

APA: antiplatelet agents

C: compliant

CCTIRS: *Comité consultatif sur le traitement de l'information en matière de recherche*

CNIL: *Commission nationale de l'informatique et des libertés*

EBD: evidence-based secondary prevention drugs

EOLE: *Etude Observationnelle de suivi Long terme post-infarctus du myocarde*

EUROASPIRE: European Action on Secondary Prevention through Intervention to Reduce Events

HR: hazard ratio

IRB: institutional review board

ITT: intent to treat

LLA: lipid-lowering agents

LOCF: last observation carried forward

MI: myocardial infarction

NC: non-compliant

SNDS: national healthcare system database

## Introduction

Short-term survival after myocardial infarction (MI) has increased over time, owing to better treatment of the acute phase and risk factors [1, 2]. As a greater number of patients with MI survive, the potential impact of secondary prevention increases. European guidelines for secondary prevention of MI are periodically updated [3-5], but the core of the prevention remains medication and lifestyle adjustment. Recommended drugs are aspirin and other antiplatelet agents (APA), beta-blockers, statins, and angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) [3-7]. In addition to drugs, patients should engage in physical activity, abstain from smoking, manage diabetes and have a Mediterranean-type diet [5, 8].

Since 1994, the European Action on Secondary Prevention through Intervention to Reduce Events (EUROASPIRE) survey, which periodically monitors how these are followed across Europe [9-11], found that despite increasing use of individual recommended drugs, treatment often failed to meet European guidelines [12]. These were established on the basis of clinical trials of individual drugs, but the effectiveness of combined medication has also been reported in global and national studies [7, 13, 14]. These studies used hospital discharge prescriptions, which may not fully describe real-life use, and had relatively short follow-ups (6 months to 1 year).

At the request of the French regulatory authorities, a cohort study was set up of the long-term survival of post-MI patients, recruited in the first three months after MI, with regular patient and prescriber reporting of treatments and of events, and ascertainment of vital status at 6 years from the national death registry.

## Methods

See supplementary material A: Methods

### Study design

EOLE (*Etude Observationnelle de suivi Long terme post-infarctus du myocarde*) is a national prospective observational cohort.

## **Main objective**

Description and quantitation of factors associated with 6-year mortality post-MI.

## **Patient population**

All the French cardiologists were invited to participate in the study, and include patients at the first outpatient consultation after discharge from hospital after an acute myocardial infarction.

Subjects were recruited within 3 months after MI, during a routine visit with a hospital or non-hospital cardiologist, from April 2006 to June 2009 (eligibility criteria in online supplementary material). This study is therefore not concerned by early post-MI mortality.

## **Outcomes**

Main outcome was all-cause death at 6 years, ascertained from contacts with patients, family, GP or cardiologists, and through a standardized legally defined procedure involving the national death registry (see supplementary material).

Secondary outcomes included cardiovascular and coronary mortality and morbidity, based on fatal and non-fatal MI, sudden death, fatal and non-fatal stroke, coronary or peripheral revascularization.

Secondary outcomes were identified from patient and physician questionnaires, hospital discharge summaries and any other relevant information. Events were adjudicated according to pre-specified criteria by an event validation committee including two cardiologists and two neurologists, blind to the patients' treatments, age, and gender.

## **Expected population size**

Based on an estimated 17% 6-year mortality, 5500 patients with recent MI ( $\leq 3$  months) followed for 6 years would yield enough events to identify a 25% difference in event rates in any group with at least 10% exposure (or non-exposure) of interest.

## **Data collection**

At inclusion investigators filled a medical questionnaire (socio-demographic data, previous medical history, cardiovascular drugs prescribed), and patients a self-administered questionnaire (drugs taken, tobacco use, lifestyle data, previous history,...).

A patient questionnaire was planned at 6 months, 2, 3, 4, 5, and 6 years. Vital status was obtained after 6 years of follow-up from the national death registry.

Full clinical information was sought for all hospitalized events by contacting the hospitals to obtain discharge summaries, and any further information as requested by the event adjudication committee.

## **Exposures**

Questionnaires queried patients and prescribers for the use or prescription of evidence-based secondary prevention drugs (EBD): beta-blockers, low-dose aspirin or other antiplatelet agents (APA), statins or other lipid-lowering agents (LLA), ACEI or ARB, and other cardiovascular or non-cardiovascular drugs.

Drug exposure was ascertained at inclusion from the cardiologist and the patient. Thereafter, only patient-reported information was used. A comparison of prescriber and patient information at inclusion (and at 2 years in some patients) found good concordance (supplementary table S1).

Patient questionnaires were considered valid if received within 2 months for the 6-month questionnaire or within 6 months of the expected date for the yearly questionnaires. Patients were sent the questionnaire before the evaluation time-point, and reminded of it at the scheduled time of the questionnaire.

## **Duration of follow-up**

Patients were followed from inclusion to 6 years or death for the main outcome, or to last information for lost to follow-up for secondary outcomes. For each event type, follow-up was censored at time of first event for that event. For death, patients were censored at 6 years (patients dying after 6 years were considered alive at last study point).

Vital status was ascertained at the end of the study period (6 years) for all patients.

## **Statistical analysis**

Main study analysis was intent to treat (ITT) considering treatment at inclusion, using multivariable analysis comparing presence to absence of the factor of interest. Each treatment's effect was compared to non-use of the given medication, adjusted on other preventive treatments and on a propensity score of exposure to that treatment at inclusion.

Patients were expected to fill regular self-questionnaires. Data from missing questionnaires were treated as follows for time-dependent analyses: if a questionnaire was missing between two existing questionnaires, and both had the same values, the missing value for a given item was considered as that of the previous questionnaire. If the values before and after were different, the missing value was treated as last observation carried forward (LOCF) or by using multiple imputations. Patients with at most one data point missing with data points available before and after the missing data point before death or end of study were considered compliant, patients with more missing data points as non-compliant.

The hazard ratios (HR) associated with all-cause death was estimated at 6 years using a Cox model with one time-dependent variable (expected patient questionnaire received), adjusted for age, gender, cardiovascular risk factors, exposure to each secondary prevention drug at inclusion and their propensity scores.

Secondary analyses were done using time-dependent analyses for exposure to each medication, adjusted on all other treatments and specific propensity scores for each of the treatments under consideration, in the compliant patients and in non-compliant patients using the different imputation methods.

In addition, observed death rates in this study were compared with expected death rates, estimated from French national data, adjusted for age, gender and duration of follow-up (standardized mortality rates).

## **Ethics**

Declaration of Helsinki



This study complies with the Declaration of Helsinki. The Committee for the protection of persons (institutional review board or IRB) considered that the study was purely observational and did not require formal approval. The National data-protection agencies (*Comité consultatif sur le traitement de l'information en matière de recherche* [CCTIRS] and *Commission nationale de l'informatique et des libertés* [CNIL]) approved the research protocol. Informed consent was obtained from all subjects. The study was monitored and accompanied by a scientific committee composed of cardiologists, epidemiologists, and a biostatistician (D. Thomas, N. Danchin, J. Tricoire, F. Paillard, S. Herberg, L. Guize<sup>†</sup>), who met regularly throughout the study.

### Study registration

This study was registered with the European Medicine Agency's EUPAS registry ([www.encepp.eu](http://www.encepp.eu)), under study number 10726.

## Results

Of the cardiologists invited to participate, 596 included 5527 patients with a recent MI. Mean age was 62.1 years, 77.6% were male. At inclusion, 99.4 % were on low-dose aspirin and/or other APA, including 97.5% on aspirin, 96.5% on statins or other LLA, 89.7% on beta-blockers and 82.4% on ACEI or ARB. Overall 72.7% were on all four EBD (Table 1). The high initial exposure rate for EBD persisted over the duration of the study among patients with data at 6 years (Table 2).

Two-thousand seven-hundred seventeen (2717) patients returned all questionnaires, 3827 returned all or almost all questionnaires (Fig. 1). Non-compliant patients were a little younger (3 years), more often active (49 vs. 59% retired), more often still smokers (13 vs. 6%), more often diabetic (19 vs. 15%) with more often a history of previous MI (14 vs. 12%) [Table 3]. They had similar initial EBD (aspirin or other APA 99 vs. 100%, statins or other LLA 95% vs. 98%), but lower rates of coronary rehabilitation programs (38 vs. 44%).

There was no difference between fully compliant patients (n = 2717) and almost fully compliant patients (n = 3827) [Table 3].

Administrative data at inclusion were complete in 5501 patients (99%). The INSEE procedure confirmed vital status at the end of the study in 4970 subjects (90%). In the 557 other patients the vital status was determined from the last known information from patient questionnaire

or from contact with family, specialist or GP at the time of study conclusion. All deaths found in the retrieval procedure had already been identified in patient follow-up.

The vital status at 6 years was therefore known in all patients, with no loss to follow up on the main study outcome.

Overall 10 228 events were reported over 6 years, 3587 considered as potentially of interest: 721 deaths and 2065 non-fatal events were adjudicated. 119 deaths were cardiovascular, 57 coronary, 64 non-coronary. There were 84 sudden deaths, and 518 deaths of non-cardiac causes or that could not be adjudicated with certainty (e.g. , found dead in bed, no autopsy) [Supplementary Table S2].

All-cause mortality was 13.1 % [95%CI 12.3-14.0] over six years in 30,823 person-years (2.34 per hundred person-years [%PY]). Coronary mortality was 0.46 %PY, cardiovascular mortality 0.66 %PY.

Death rates were stable over study follow-up time. Other events were more common in the first year of follow-up (Fig. 2).

Compared to the expected all-cause death rate in the general population, standardized mortality rates in EOLE were 1.11 [1.03-1.20] overall, 1.05 [0.97-1.15] in men, and 1.29 [1.12-1.48] in women.

Factors associated with all-cause death in multivariable propensity score adjusted analyses were, by decreasing strength of association (Table 4), age, non-compliance to study protocol; smoking at inclusion; previous MI; diabetes; and high blood pressure.

Among the secondary prevention drugs reported at inclusion, in this intent to treat analysis beta-blockers and statins were associated with a significantly lower risk of death. The other drugs had HR between 0.8 (aspirin) and 1.0 (ACEI) with wide confidence intervals that included 1; coronary rehabilitation programs were associated with lower mortality.

Time-dependent analysis in patients who returned all or almost all expected questionnaires (as-treated analysis), found no statistically significant effect of any of the preventive treatments (Table 5). When LOCF with 6-month censor after last questionnaire was applied for missing information, more patients were available for analysis, the confidence intervals became narrower, and Statins and ACEI became associated with a lower risk of overall mortality (Table 5). Neither beta-blockers (HR 1.1 [0.87-1.39]) nor antiplatelet agents (HR 0.94 [0.69-1.30]) were associated with lower mortality.

Of the 2768 non-fatal events of interest recorded during the study, 1065 were coronary events and 1064 were other cardiovascular events. The most common coronary events were angina

pectoris without revascularization, and revascularization without acute coronary syndrome. They are described in supplementary Table S3.

Survival analysis (Fig. 1) showed a sharp increase in event rates during the first 6 months, related in part to revascularization procedures, with stable event rates thereafter. However the number of events for most outcomes and the number of unexposed subjects were too low for stable estimates of risks or benefits on these outcomes.

Patients with missing questionnaires also had higher cause-specific morbidity and mortality (supplementary Table S4).

## Discussion

In this long-term post-MI survival study, age, diabetes, smoking, and previous MI were predictors of all-cause death. There was no association with a history of hypertension or hypercholesterolemia, probably because of the very high prevalence of use of antihypertensive and lipid lowering drugs. Cardiac rehabilitation programs decreased the risk of death, as did prescription of beta-blockers and statins at inclusion. Non-compliance to the study protocol (at least one non-returned questionnaire) was associated with a three-fold higher risk of dying. These patients were more often still professionally active, still smokers at inclusion, and fewer participated in cardiac rehabilitation programs. The prescription and reported use of prevention medication were high, though always a few percentage points lower than in study-compliant patients. The effect of non-compliance persisted when known risk factors were taken into account such as drug exposure or rehabilitation programs. Non-compliance to study protocol probably reflects general non-compliance with disease management. It might be associated also with other unmeasured confounders or risk modifiers, but certainly these patients represent a behaviourally high-risk population, and should be especially closely monitored and managed.

Post-MI patients had very high exposure to evidence-based medicines, reaching 99% for aspirin at inclusion. Because of the lack of unexposed subjects, the effect of drugs was very difficult to measure. In a traditional intent-to-treat analysis taking into account all available data using exposure at inclusion adjusted on propensity scores for each treatment, we found a protective effect only of beta-blockers and statins at inclusion.

An as treated approach using time-dependent drug exposure in patients with enough exposure data found a protective effect of statins and ACE inhibitors.

Beta-blockers, which did confer a benefit in the intent to treat analysis, no longer had an effect in the as-treated analysis. Bezin (2017) found that whether beta-blockers are or not included in the secondary prevention regimen does not change overall mortality, using different analytical models [15]. In contrast for instance the inclusion of statins in the treatment was associated with a 30% lower occurrence of MACE or mortality, whether the model is fixed-time model (ITT) or any of the three time-dependent models. These results concur with those of Puymirat et al [16] who found that there was a short-term benefit with beta-blockers (which might correspond to what we found in the ITT model), but no long-term benefit in patients without heart failure, beyond the first few months. On the other hand, Neumann et al [17] found an increased occurrence of hospital readmissions for ACS after stopping beta-blockers in optimally treated patients without heart failure. An increase in all-cause death was not significant. Others have also found that long-term beta-blockers were not associated with lower death rates [18, 19]. The potential biases in observational studies, related to the reasons for stopping beta-blockers, make it difficult to conclude. This would certainly justify a proper large randomized controlled trial of beta-blockers cessation in patients without heart failure, after a pre-specified delay after initial ACS, such as one year

The benefits of aspirin at the acute phase of MI seem indisputable [20-22], but longer-term benefits are less certain [23], with a possible difference between men and women, which may contribute to the higher mortality we also found in women [24, 25]. Aspirin has been associated with positive outcomes in secondary prevention [22, 26], less so in primary prevention. We found no clear benefit in aspirin users compared to non-users in intent to treat or per-treatment analyses, despite a 25% lower event rate. However, there were very few non-users, especially of aspirin, with as a result very wide confidence intervals. Bezin (2017) found that in ITT APA did not have an effect, with the same power issues [15]. A 15% risk reduction in their time-dependent model (model 1) was not significant, presumably because of little non-exposed time (exposure to APA included 80% of all person-time). In the last two models, APA did have a protective effect.

The protection by non-aspirin antiplatelet agents (APA) is consistent with clinical trials, which demonstrated benefit of APA when added to aspirin [8]. Studies in large population databases, using modern analytical methods, could give further indications as to the relative merits of the individual treatments, or their associations [15, 27, 28].

ACEI or ARB were not protective in the ITT analyses, but were in the time-dependent analyses. Others have found in long-term as-treated studies that, compared to the full four-treatment regimen, not using statins or ACEI was associated with increased mortality, results similar to those found here [15].

The outcome rates were very low, not different for mortality from that expected in the general population of similar age distribution. The combination of low event rates and very low non-exposure rates threw off the initial study size computations, based on the older data that was available when the study was designed. This confirms the effectiveness of modern management of myocardial infarction, and the compliance to recommendations, but on the other hand will impose clearly larger studies or clinical trials, making such studies more difficult to fund and perform.

The main weakness of this study of long-term mortality after MI is its observational nature. Because treatments were chosen by prescribers, and not randomly attributed, there was no possibility of adjusting sample sizes for exposure and non-exposure, resulting in very low numbers of unexposed patients. In addition, because of the non-random treatment allocation, the characteristics of patients treated or not with the various therapeutic options or evidence-based medicines could be different, even though most patients were common to all treatments. The less strict control of patient participation may have resulted in higher patient non-compliance than in a clinical trial, which rendered per treatment analyses less easy because of missing exposure data during follow-up.

The representativeness of the population could also be discussed: since patient recruitment was done by the cardiologists, there may have been patient selection, as is common in field studies. From the national healthcare system database (SNDS) [29] there are about 50 000 MI yearly in France, of whom EOLE represent over the 3 year inclusion period about one in 25 (4%). Our patients were on average 62 years old and 78% were male. The description of MI in France over that period may be found in studies in the national healthcare database. For instance, Bezin et al. looked at ACS and MI from 2004 to 2007, and found 71% males with MI, average age 62, compared to mean age 66, 70% male for all ACS [30]. In a later study on ACS, the same authors found a mean age of 67, with 67 %male [15]. In another study in the whole database, in 2013 we found in 54000 ACS, mean age 67, 71% male.

The patients in EOLE were a little younger than the whole ACS population, but the same age as the MI population nationwide [15, 27, 30]. They were slightly more often male, which is consistent with over-representation of men in field studies and clinical trials.

They were closer for instance to the PLATO study of ticagrelor vs. clopidogrel post-MI (mean age 62, 28% female). This may be related to inclusion criteria, or to patient preference not to participate in studies. In addition, in contrast to database studies where the information is present independent of patient participation or not, patients in field studies may have missing data, which might by itself be informative.

On the other hand a strength of this study is its setting: being a field study, there was extensive clinical information at inclusion on potential confounders. It had features commonly found in clinical trials: regular patient and data monitoring, blinded adjudication of all events of interest with hospital discharge information for over 96% of the events. Of course we cannot exclude that some events may not have been reported by patients or their physicians, but this is unlikely for major cardiovascular events. Death, the main outcome, was ascertained using a standard validated procedure, even for patients who were lost to follow-up or non-compliant with questionnaires, so that there is no missing data on the main outcome [31, 32]. Exposure data came from prescriber and patient questionnaires, which were highly concordant. High long-term use of secondary prevention treatment has already been reported in France using claims databases [15, 27]. Treatment was generally in line with the national and European recommendations [33].

## Conclusion

This prospective long-term study of post-MI all-cause mortality found that beyond known predictors such as age, diabetes or previous MI, poor patient compliance with the study procedures was strongly associated with excess deaths. This is probably a proxy for general non-compliance with secondary prevention or cardiovascular management best practices.

The analyses of the benefits associated with evidence-based drugs for secondary prevention in ITT or in time-dependent analyses showed the ones associated with lower death rates were statins and beta-blockers for ITT, statins and ACE inhibitors (or ARB) per-treatment. However, low event rates and small numbers of unexposed patients resulted in low study power for these analyses. The death rate in men was close to that of the age and sex-adjusted general population. Excess residual mortality in women remains a matter of concern.

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All authors had the opportunity to review and approved the final version of the paper, as submitted. Patient representatives were not consulted to prepare or execute this study.

## Disclosure of interest

CD, PB, CDP, EG, HM, MAB and NM report no conflicts of interest

DT reports personal compensation as member of the scientific committee of this study from PIERRE FABRE during the conduct of the study. He has received personal fees from Novartis, Johnson & Johnson, Chiesi, Lilly and Astra-Zeneca.

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**Legend to the figures**

**Figure 1.** Patient disposition.

**Figure 2.** Time to first event after inclusion.

**Table 1.** Patient characteristics at inclusion.

|  | n = 5527    |
|--|-------------|
| Gender, male – n (%)                                       | 4288 (77.6) |
| Age, years – mean (SD)                                     | 62.1 (13.3) |
| BMI  |             |
| <18.5  | 56 (1.0)    |
| [18.5-25[  | 1953 (35.3) |
| [25-30[  | 2419 (43.8) |
| [30-35[  | 837 (15.1)  |
| ≥35  | 215 (3.9)   |
| Employed, n (%)  | 2193 (39.7) |
| Current smoker, n (%)                                      | 531 (9.6)   |
| LVEF <40%, n (%)   | 450 (8.1)   |
| Diabetes, n (%)  | 921 (16.7)  |
| Previous history of hypercholesterolemia, n (%)            | 2467 (44.6) |
| Previous history of hypertriglyceridemia, n (%)            | 848 (15.3)  |
| Previous history of high blood pressure, n (%)             | 2409 (43.6) |
| Time from MI to inclusion, days – mean (SD)                | 34.1 (27.6) |
| First MI – yes, n (%)                                      | 4792 (86.7) |
| MI criteria, n (%)   |             |
| Symptomatic: characteristic pain                           | 5376 (97.3) |
| Electrical <sup>a</sup>                                    | 4513 (81.7) |
| Enzymatic <sup>b</sup>                                     | 5061 (91.6) |
| Number of MI criteria, n (%) <sup>c</sup>                  |             |
| 2  | 1631 (29.5) |
| 3  | 3896 (70.5) |
| Cardiovascular rehabilitation program, n (%)               | 2240 (40.5) |
| Use of secondary prevention treatments at inclusion, n (%) |             |
| Beta-blockers  | 4957 (89.7) |
| Aspirin or other APA                                       | 5496 (99.4) |

|  |             |
|--|-------------|
| aspirin                                    | 5388 (97.5) |
| other APA                                  | 5032 (91.0) |
| ACEI or ARB                                | 4557 (82.4) |
| ACEI                                       | 4033 (73.0) |
| ARB  | 673 (12.2)  |
| Statins or other LLA                       | 5335 (96.5) |
| statins                                    | 5297 (95.8) |
| other LLA                                  | 249 (4.5)   |
| Exposure to all four prevention treatments | 4019 (72.7) |

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<sup>a</sup>Q wave in  $\geq 2$  adjacent leads and/or ST segment elevation in  $\geq 2$  adjacent derivations

<sup>b</sup>elevated CPK-MB and/or elevated troponin

<sup>c</sup>symptomatic, ECG, or enzymatic

ACEI: angiotensin converting enzyme inhibitors; APA: antiplatelet agent; ARB: angiotensin receptor blockers; BMI: body mass index; LLA: lipid-lowering agents; LVEF: left ventricular ejection fraction; MI: myocardial infarction

**Table 2.** Exposure to evidence-based drugs at inclusion and at 6 years post-MI in patients with 6-year questionnaires available

| n = 3308                    |                       |                     |
|-----------------------------|-----------------------|---------------------|
|                             | Exposure at inclusion | Exposure at 6 years |
| Beta-blockers, n (%)        | 2659 (80.4)           | 2569 (77.7)         |
| Aspirin or other APA, n (%) | 2952 (89.2)           | 3118 (94.3)         |
| Statins or other LLA, n (%) | 2903 (87.8)           | 3000 (90.7)         |
| ACEI or ARB, n (%)          | 2451 (74.1)           | 2586 (78.2)         |

ACEI: angiotensin converting enzyme inhibitors; APA: antiplatelet agent; ARB: angiotensin receptor blockers;

LLA: lipid-lowering agents.

**Table 3.** Description of patients who were fully (all questionnaires returned), almost fully compliant (at most one missing questionnaire) or non-compliant.

|                                       | Fully compliant |                 | Fully or almost fully compliant |                 |
|---------------------------------------|-----------------|-----------------|---------------------------------|-----------------|
|                                       | No<br>n = 2810  | Yes<br>n = 2717 | No<br>n = 1696                  | Yes<br>n = 3827 |
| Male, n (%)                           | 2150 (76.5)     | 2138 (78.7)     | 1287 (75.9)                     | 2998 (78.3)     |
| Age (median, years)                   | 60.0            | 63.0            | 60.0                            | 62.0            |
| Retired, n (%)                        | 1371 (48.8)     | 1600 (58.9)     | 839 (49.5)                      | 2130 (55.7)     |
| BMI > 30 kg/m <sup>2</sup> , n (%)    | 552 (19.6)      | 500 (18.4)      | 336 (19.8)                      | 716 (18.7)      |
| Smoker at inclusion, n (%)            | 372 (13.2)      | 159 (5.9)       | 254 (15.0)                      | 277 (7.2)       |
| Diabetes, n (%)                       | 522 (18.6)      | 399 (14.7)      | 345 (20.3)                      | 576 (15.1)      |
| Previous MI, n (%)                    | 405 (14.4)      | 329 (12.1)      | 270 (15.9)                      | 464 (12.1)      |
| Treatment at inclusion, n (%)         |                 |                 |                                 |                 |
| Beta-blockers                         | 2493 (88.7)     | 2464 (90.7)     | 1483 (87.4)                     | 3470 (90.7)     |
| Aspirin or other APA                  | 2791 (99.3)     | 2705 (99.6)     | 1680 (99.1)                     | 3812 (99.6)     |
| Statins or other LLA                  | 2682 (95.4)     | 2653 (97.6)     | 1605 (94.6)                     | 3726 (97.4)     |
| ACEI or ARB                           | 2297 (81.7)     | 2260 (83.2)     | 1377 (81.2)                     | 3176 (83.0)     |
| Coronary rehabilitation program n (%) | 1054 (37.5)     | 1186 (43.7)     | 604 (35.6)                      | 1632 (42.6)     |

ACEI angiotensin converting enzyme inhibitors; APA antiplatelet agents; ARB: angiotensin receptor blocker; BMI: body mass index; LLA: lipid-lowering agents; MI: myocardial infarction



**Table 4.** Hazard ratios of factors associated with all-cause death after 6 years of follow-up post-MI, intent to treat analysis (n = 5512<sup>a</sup>)

|   | Alive <sup>a</sup><br>n = 4792 | Dead <sup>a</sup><br>n = 720 | HR <sup>b</sup><br>[95% CI] |
|---|--------------------------------|------------------------------|-----------------------------|
| <b>Missing questionnaires<sup>c</sup></b> |                                |                              | <b>3.13 [2.63-3.57]</b>     |
| <b>Male, vs. Female</b>                   | 3760 (78.5)                    | 517 (71.8)                   | 1.17 [0.97-1.41]            |
| <b>Age, vs. &lt; 50 years</b>             |                                |                              |                             |
| 50-59 years                               | 1359 (28.4)                    | 72 (10.0)                    | 1.50 [1.01-2.22]            |
| 60-69 years                               | 1100 (23.0)                    | 114 (15.8)                   | 3.06 [2.10-4.46]            |
| 70-79 years                               | 979 (20.4)                     | 240 (33.3)                   | 6.94 [4.77-10.12]           |
| ≥ 80 years                                | 334 (7.0)                      | 254 (35.3)                   | 15.72 [10.67-23.15]         |
| <b>Diabetes</b>                           | 736 (15.4)                     | 183 (25.4)                   | 1.39 [1.17-1.65]            |
| <b>History of arterial hypertension</b>   |                                |                              |                             |
| Moderate                                  | 1628 (34.0)                    | 364 (50.6)                   | 1.20 [1.02-1.42]            |
| Severe                                    | 337 (7.0)                      | 75 (10.4)                    | 1.15 [0.88-1.50]            |
| <b>Previous MI</b>                        | 576 (12.0)                     | 157 (21.8)                   | 1.46 [1.22-1.75]            |
| <b>Smoking</b>                            |                                |                              |                             |
| Stopped before MI                         | 1329 (27.7)                    | 247 (34.3)                   | 1.23 [1.02-1.48]            |
| Stopped between MI and inclusion          | 1400 (29.2)                    | 105 (14.6)                   | 1.47 [1.13-1.92]            |
| Smoker at inclusion                       | 476 (9.9)                      | 53 (7.4)                     | 1.76 [1.27-2.44]            |
| <b>Hypercholesterolemia</b>               | 2130 (44.4)                    | 333 (46.3)                   | 0.94 [0.81-1.10]            |
| <b>Coronary rehabilitation program</b>    | 2071 (43.2)                    | 166 (23.1)                   | 0.74 [0.62-0.89]            |
| <b>EBD Exposure at inclusion</b>          |                                |                              |                             |
| Beta-blockers                             | 4347 (90.7)                    | 597 (82.9)                   | 0.79 [0.64-0.96]            |
| Aspirin or other APA                      | 4774 (99.6)                    | 707 (98.2)                   | 0.75 [0.42-1.33]            |
| Statins or other LLA                      | 4666 (97.4)                    | 655 (91.0)                   | 0.68 [0.51-0.90]            |

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|             |             |            |                  |
|-------------|-------------|------------|------------------|
| ACEI or ARB | 3957 (82.6) | 586 (81.4) | 0.95 [0.78-1.15] |
|-------------|-------------|------------|------------------|

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<sup>a</sup>Number of patients with available data;

<sup>b</sup>HR hazard ratio adjusted on all variables present in the model, including individual propensity scores for each drug;

<sup>c</sup>time-dependent variable with multiple changes;

ACEI: angiotensin converting enzyme inhibitors; APA: antiplatelet agent; ARB: angiotensin receptor blocker; EBD: evidence-based drugs; LLA: lipid lowering agent; MI: myocardial infarction.

**Table 5.** Hazard ratios associated with evidence-based secondary prevention treatment for all-cause mortality during 6 years of follow-up, using time-dependent analyses in patients with all or almost all questionnaires, and in all patients with analysable data; As-treated analysis.

| Exposed versus non-exposed | Fully or almost fully compliant patients;<br>adjusted HR [95% CI]*<br>n=3821 | All available usable points using LOCF with 6-month censure;<br>adjusted HR [95% CI]*<br>n= 5516 |
|----------------------------|--|--|
| Beta-blockers              | 1.07 [0.79-1.44]   | 1.10 [0.87-1.39]   |
| Aspirin and/or other APA   | 0.94 [0.62-1.43]   | 0.94 [0.69-1.30]   |
| Statins and/or other LLA   | 0.72 [0.51-1.03]   | 0.73 [0.56-0.96]   |
| ACEI or ARB                | 0.86 [0.65-1.15]   | 0.75 [0.60-0.93]   |

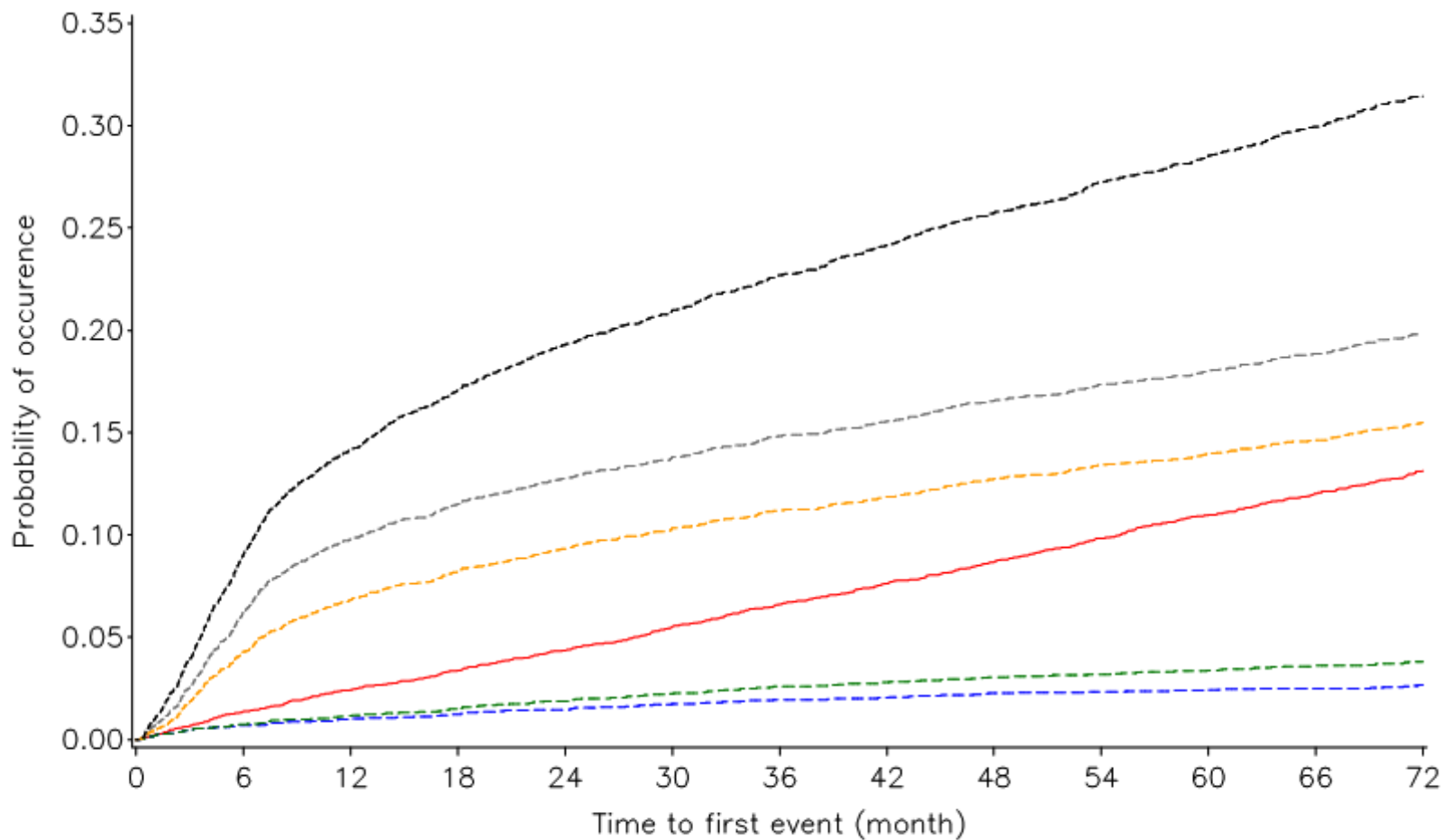
\*HR adjusted on propensity scores for exposure at inclusion, on propensity scores for exposure at each time point, on age, gender, diabetes, high blood pressure, hypercholesterolemia and smoking;

ACEI: angiotensin converting enzyme inhibitors; APA: antiplatelet agents; ARB: angiotensin receptor blockers; LLA: lipid-lowering agents; LOCF: last observation carried forward.

**Figure 1.** Patient disposition

|   | Yes  | No   |
|---|------|------|
|   | N =  | N =  |
| All patients included                                       | 5527 |      |
| Fully compliant with all data points present                | 2717 | 2817 |
| Fully or almost fully compliant (at most one missing point) | 3827 | 1696 |
| With usable data (LOCF with 6-month censure)                | 5516 | 11   |
| With primary outcome data (all-cause death)                 | 5527 | 0    |

LOCF: last observation carried forward



\* events of interest

\*\* events of interest (including sudden deaths) with confirmed, probable or possible causality