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**ORIGINAL ARTICLE**
*Acute coronary syndromes*

# Adherence to agents acting on the renin–angiotensin system in secondary prevention of non-fatal myocardial infarction: a self-controlled case-series study

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**Aims** In accordance with current guidelines, patients discharged after acute myocardial infarction (AMI) are usually prescribed agents acting on the renin–angiotensin system (ACE-I/ARB). However, adherence to prescribing medications is a recognized problem and most studies demonstrating the value of adherence were limited by their non-randomized design and by 'healthy-adherer' bias. Herein we sought to evaluate the relationship between adherence to ACE-I/ARB and risk of subsequent AMIs, by using the self-controlled case-series design which virtually eliminates interpersonal confounding, being based on intrapersonal comparisons.

**Methods and results** We linked data from three longitudinal registries containing information about hospitalizations, drug prescriptions, and vital status of all residents in an Italian region. From 30 089 patients hospitalized for AMI in the years 2009–11, we enrolled the 978 with non-fatal re-AMIs at Days 31–365 after discharge, receiving at least one ACE-I/ARB prescription collected at any of the regional pharmacies. Using information on prescriptions, each individual's observation time was then divided into periods exposed or unexposed to ACE-I/ARB. The relative re-AMI incidence rate ratios (IRRs) of ACE-I/ARB exposure were estimated by conditional Poisson regression. During drug-covered periods, the risk of AMI recurrence was ∼20% lower, i.e. the IRR (rate of recurrent AMI in exposed versus unexposed periods) was 0.79 (95% CI 0.66–0.96, $P = 0.001$). The benefit of ACE-I/ARB was confirmed also by sensitivity analyses considering only first recurrences, excluding cases with AMI within previous 3 years, or with long, not AMI, hospital re-admission.

**Conclusions** Poor adherence to ACE-I/ARB prescription medication was associated with a 20% increased risk of recurrent AMI. This was consistent with previous research, but the SCSS study design, even if not randomized, eased previous concerns about healthy-adherer bias.

**Keywords** AMI • ACE-I • ARB • Adherence

## Introduction

Patients discharged from hospital after acute myocardial infarction (AMI) are usually prescribed numerous medications intended for life-long use, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ACE-I/ARB). The evidence underlying the benefit of these medications is robust.[1] However, adherence to prescribing medications is a recognized problem[2,3] and showing that poor adherence is associated with worse outcomes may help to underpin the ongoing efforts to improve medication adherence.[4] In general, most studies demonstrated the value of adherence to cardiovascular drugs after AMI; however, at the same

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time, they were limited by their non-randomized design and possible bias due to confounded interpersonal comparisons (i.e. healthy-adherer effect).[5,6]

A study design that allows enhanced control over confounding arising from variables that are constant within an individual, such as the 'healthy-adherer effect', is the self-controlled case-series (SCCS).[7] Self-controlled case-series and other case-only designs are increasingly used in post-licensure pharmacoepidemiological studies because each individual acts as his/her own control, eliminating the possibility of interpersonal confounding.[8,9]

For these reasons, we decided to undertake an SCSS study to investigate the effects of adherence to ACE-I/ARB in the secondary prevention of AMI. The primary hypothesis is that, given the experimental evidence in favour of these drugs, poor adherence to prescription is associated with increased AMI recurrence.

# Methods

## Setting and participants

The study was conducted in Emilia-Romagna, a wealthy Italian Region with 4.5 million inhabitants and a surface of 22000 km$^2$. The Region has 61 hospitals admitting acute patients and 14 hospitals performing interventional cardiology.

We initially selected all of the patients who were admitted in any of the regional hospitals with a diagnosis of AMI in the four calendar years 2009–12. Subsequently, we included those who suffered from at least another episode of AMI in the 365 days after the discharge from their index AMI hospital admission. We excluded patients whose re-infarction occurred within 30 days of discharge from the index AMI hospital admission. This exclusion was made for two reasons. First, additional percutaneous coronary interventions (PCIs) are sometimes staged shortly after discharge and an admission for this reason could have been classified as a new AMI episode. Second, the assessment of exposure in the first weeks may be faulty because before discharge patients are sometimes given a small supply of drugs that is not recorded by the hospital pharmacy (see below for the description of exposure assessment). We then excluded patients who died of cardiovascular causes during the observation period. The justification is explained in the paragraph below on statistics. Finally, we considered only patients with at least one prescription for ACE-I/ARB in the year after discharge.

According to our institutional rules, neither patient consent nor ethics committee approval was necessary, given the observational, retrospective design of the study and the anonymity of the databases provided to the researchers.

## Data sources, outcome, and exposure assessment

We linked data at an individual level from three region-wide longitudinal registries managed by the Emilia-Romagna Regional Health Agency. The Hospital Discharge Registry contains the usual so-called administrative information recorded in the charts of all the regional hospitals. The Prescription Drug Registry collects information on dates, dosage, and quantities for every prescription dispensed within the regional boundaries, from both hospital and community pharmacies. The Demographic Registry holds information on age, sex, date of birth, place of residence, and vital status of all residents in Emilia-Romagna. A unique patient identifier allowed cross-linking between the databases.

Through the Hospital Discharge Registry we identified the initial study population, i.e. all individuals with an episode of hospital admission with an ICD-9-CM code 410.x1 in any position. The same definition was used for the other MI episodes. From this registry, we also collected the other clinical information (e.g. demographics, dates of events, etc.).

Using the Prescription Drug Registry, we identified for each participant all the prescriptions for ACE-I/ARB—anatomical-therapeutic-chemical-classification system (ATC) Class C09—collected at any of the regional pharmacies for 1 year after discharge from the index AMI episode. We then computed the number of days covered by ACE-I/ARB prescriptions as the total number of defined daily doses (DDDs) prescribed to each individual. The DDD is a technical unit of measurement, used by the World Health Organization, which reflects the average adult dose used for the main indication as reflected by the ATC code dispensed packs. If a patient refilled a prescription early, the number of days covered was still calculated according to the DDD of the previous prescription, allowing for stockpiling.

Each individual's observation time was then divided into exposed or unexposed periods according to the above information. ACE-I/ARB are short-acting drugs and they do not accumulate; therefore, we felt it appropriate not to account for wash-out or intermediate-risk periods.

Prescriptions filled for concomitant cardiovascular therapy, β-blockers (ATC class C07), statins (ATC class C10AA), acetylsalicilic acid, ticlopidine, and clopidogrel (B01AC04, B01AC05, and B01AC06) were evaluated at any time from 1 month to 12 months after hospital discharge.

We used the Demographic Registry to record any deaths occurring during the observation period and their causes. A death was defined as being of cardiovascular origin if any of the following codes were recorded: ICD9-CM 410-414, 425-438, 798-799; ICD10 I20-I25, I39-I52, I60-I69, and R96-R99.

Comorbidities were ascertained by means of ICD9-CM codes from co-diagnosis at discharge within 5 years before the index AMI episode.

## Statistical analyses

The SCSS method relies on intrapersonal comparisons in a population of individuals who have both the outcome and exposure of interest. The rate of events during exposed periods of time is compared with the rate during unexposed time periods. This method removes the potential confounding effect of characteristics that vary between individuals, such as unmeasured risk factors for cardiovascular disease.

We compared the incidence of AMI in the time periods covered and not covered by medication during Days 31–365 (or earlier in the case of death) following discharge from the index AMI hospital admission. *Figure 1* provides a graphics display of the study design. We estimated the relative incidence rate ratios (IRRs) using conditional Poisson regression with Stata software, version 13 (Stata Corp, College Station, TX, USA). Incidence rate ratios compare the rate of events during exposed periods of time with the rate during all other observed time periods. Because the SCSS method samples only cases, the estimation is within individuals, wherefore a conditional Poisson model is required and the method can produce estimates of relative incidence only, rather than absolute incidence. It is then inappropriate to simply juxtapose the number of events with the total sum of individuals' person-time, like in the cohort design.

Although the observation period was relatively short, we preferred to adjust for possible intrapersonal time-trends of both adherence (e.g. decreasing with time[10]) and re-infarction risk (e.g. increasing with time/age) by dividing the observation period in two semesters and adding this term to the model.

The SCSS method and its underlying Poisson distribution require some assumptions about the distribution of events. The most important is that the occurrence of an event (i.e. the outcome) must not alter the probability of subsequent exposure. The most extreme setting in which

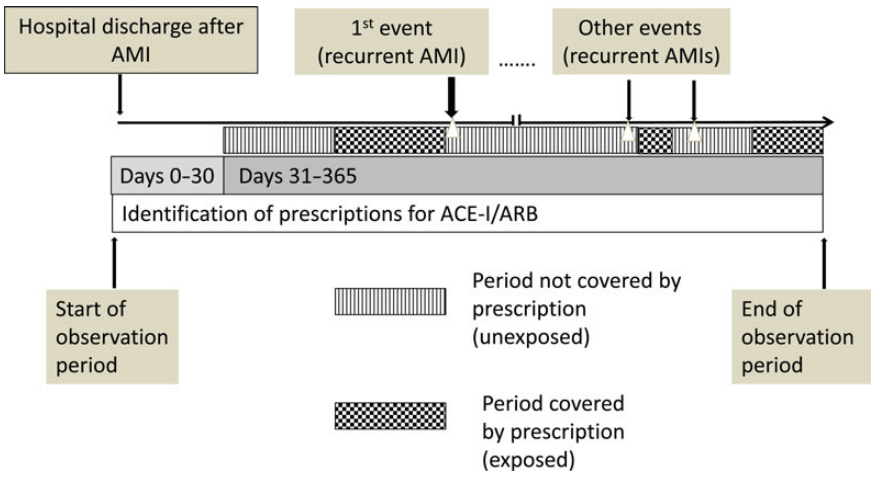


**Figure 1** Pictorial representation of study design. The hypothetical patient of this figure would contribute to the confirmation of the benefits of the ACE-I/ARB therapy because he experienced the acute myocardial infarction recurrences while not covered by medication. For further mathematical details on the computation of the incidence rate ratio see Ref.[7] AMI, acute myocardial infarction; ACE-I/ARB, agents acting on the renin–angiotensin system.

this assumption fails is when the event of interest is death, because individuals cannot be exposed after death. In other words, observation periods of individuals should end independently of the timing of the outcome. If the outcome increases the short-term risk of death, as in the case of AMI, this assumption is violated. One possibility would be to use a recently developed extension of the method.[11] However, this proved impractical for our data because of the many crossovers (i.e. time intervals with different exposure status) occurring during the observation period. We decided to overcome the problem by excluding all cases in which patients died due to cardiovascular causes during the observation period, because their outcome-censored follow-up could have biased the estimates. The same strategy has been adopted elsewhere.[12]

A less extreme violation of the main assumption could also occur if the first occurrence of the outcome had any influence on subsequent exposure. Clearly, this could be the case in our study, as patients might improve their adherence after the warning of an AMI recurrence. To evaluate whether the occurrence of a re-infarction had any influence on the patients' compliance with medication prescription, we measured the proportion of exposed and unexposed days in the observation period before and after the first re-infarction. We then compared these proportions with the Wilcoxon signed rank test. If the proportions were significantly different, we attempted to quantify the resulting bias through a sensitivity analysis that considered only first events (i.e. only the first AMI recurrence).

Finally, we conducted two more sensitivity analyses:

(i) During hospital admissions, patients may receive medications that go undetected by the Prescription Drug Registry. To verify the possible effects on our exposure assessment, we excluded all individuals who had been hospitalized for >5 days (except the AMI admissions) during the observation period.

(ii) We excluded those who had suffered from a previous AMI in the 3 years before their index AMI in order to analyse the effect of exposure in as many patients as possible with first AMI occurrence.

# Results

The flow diagram of the study population is shown in *Figure 2*.

We identified 978 patients satisfying the eligibility criteria who underwent hospitalization for non-fatal re-AMI between January 2009 and December 2012 in the Emilia-Romagna region of Italy.

The characteristics of the study population are shown in *Table 1*. The median age was 78 years and males were predominant (64%). Non ST-elevation myocardial infarction was the most frequent form of re-AMI (648 patients, 66.3%). Six hundred and twenty-eight (64.2%) patients underwent in-hospital myocardial revascularization (PCI/coronary artery bypass). About 40% of the patients were diabetic.

As reported in *Table 2*, the majority of individuals (88%) experienced only one re-AMI during the observation period, while the maximum number of re-AMI episodes was 4. The non-cardiovascular mortality during the study period was 7.2%. The overall adherence, in terms of mean percentage of exposed days during the observation period, was 75.5%. *Table 3* shows the study population 1-year post-discharge medication use for β-blockers, statins, and antiplatelet agents.

As reported in *Table 4*, there were, respectively, 754 and 262 events during exposed (i.e. with ACE-I/ARB coverage) and unexposed (i.e. without ACE-I/ARB coverage) periods. The relative risk (IRR) was 0.79 (95% CI 0.66–0.96, $P = 0.01$). As expected, the percentages of exposed days after the first AMI recurrence was significantly higher (80.0 vs. 70.1%, $p$ of the Wilcoxon signed rank test <0.01). However, when only first events were considered, the relative risk (IRR) was similar: 0.71 (95% CI 0.59–0.87, $P <$ 0.01). Of note, after exclusion of patients with long (>5 days) hospitalization, the benefits of ACE-I/ARB were more significant: IRR 0.38 (95% CI 0.25–0.58, $P < 0.01$).

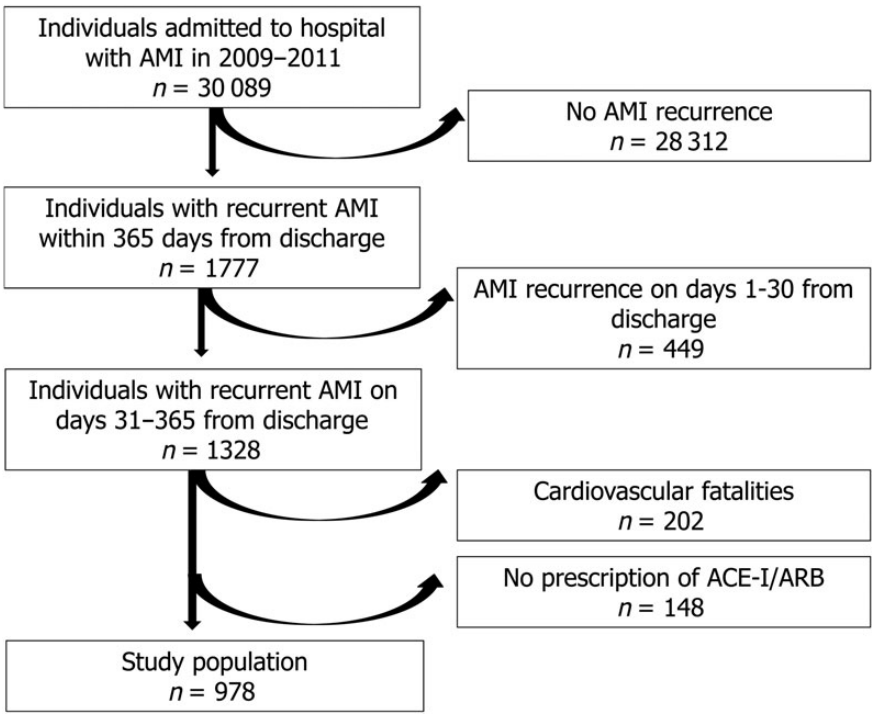


**Figure 2** Flow diagram of study population. Acute myocardial infarction indicates acute myocardial infarction, ACE-I/ARB indicates agents acting on the renin–angiotensin system.

**Table 1 Clinical and demographic characteristics of the study population**

| | |
|---|---|
| No. of cases | 978 |
| Age (years) median (interquartile range) | 78 (69–84) |
| Gender: male, *n* (%) | 632 (64.6) |
| Index AMI characteristics | |
| NSTEMI, *n* (%) | 648 (66.3) |
| Revascularization (PCI and/or CABG), *n* (%) | 628 (64.2) |
| Recurrent AMIs characteristics | |
| NSTEMI, *n* (%) | 883 (79.4) |
| Revascularization (PCI and/or CABG), *n* (%) | 792 (69.4) |
| Hypertension, *n* (%)[a] | 403 (41.2) |
| Diabetes, *n* (%)[a] | 380 (38.9) |
| Dyslipidemia, *n* (%)[a] | 151 (15.4) |
| Atrial fibrillation/flutter, *n* (%)[a] | 82 (8.4) |
| Valvular heart disease, *n* (%)[a] | 56 (5.7) |
| Chronic obstructive pulmonary disease, *n* (%)[a] | 176 (18.0) |
| Cancer, *n* (%)[a] | 88 (9.0) |
| Heart failure, *n* (%)[a] | 150 (15.3) |
| Chronic renal disease, *n* (%)[a] | 100 (10.2) |
| Peripheral arterial disease, *n* (%)[a] | 112 (11.5) |
| Cerebral vascular disease, *n* (%)[a] | 160 (16.4) |

NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneuos coronary intervention; CABG, coronary artery bypass graft revascularization.
[a]Five years before the index hospitalization.

**Table 2 Non cardiovascular mortality, acute myocardial infarction recurrence, and treatment exposure of the study population**

| | |
|---|---|
| No. of patients | 978 |
| Non-cardiovascular mortality[a], *n* (%) | 70 (7.2) |
| Patients with AMI recurrences during the observation period, *n* (%) | |
| 1 | 865 (88.5) |
| 2 | 98 (10.0) |
| 3 | 9 (0.9) |
| 4 | 6 (0.6) |
| Length of observation period (days), mean ± SD | 358 ± 33 |
| Exposed to ACE-I/ARB (drug coverage) | 264 ± 99 |
| Unexposed to ACE-I/ARB (no drug coverage) | 100 ± 98 |

AMI, acute myocardial infarction; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.
[a]Patients who died of cardiovascular causes were excluded; see Methods for details.

The exclusion of the 50 cases with a previous MI during the 3 years before their index admission did not change the estimates: IRR 0.79 (95% CI 0.65–0.96, $P < 0.01$).

## Discussion

We found that poor adherence to ACE-I/ARB prescription medication after hospital discharge for AMI was associated with an

increased risk of recurrent AMI. During drug-covered periods, the risk of AMI recurrence was about 20% lower.

Experimental evidence suggests that ACE-I/ARB reduce the risk associated with atherosclerotic cardiovascular disease through 'cardioprotective' (benefits in overall cardiac haemodynamics, energetics, electrical stability, and the reduction in left ventricular mass) and 'vasculoprotective' effects (direct anti-proliferative effects, possible anti-atherogenic properties, and favourable effects on thrombotic mechanisms and on arterial compliance and tone).[13]

ACE-I/ARB probably exert these protective effects by blocking both circulating and tissue renin–angiotensin systems.

Evidence from randomized trials has shown that ACE-I reduce mortality from AMI particularly in the presence of heart failure, left ventricular systolic dysfunction (left ventricular ejection fraction <40%), anterior location of the AMI, and abnormal wall motion score index.[14]

In addition, in post-AMI patients with asymptomatic left ventricular dysfunction, long-term administration of captopril reduces recurrence of AMI and the need for cardiac revascularization independently of left ventricular ejection fraction, suggesting either an anti-ischaemic effect or the ability of the angiotensin-converting enzyme inhibitor to modify the atherosclerotic process in survivors of AMI.[15]

Moreover, a reduction in the rates of mortality and vascular events (myocardial infarction, myocardial revascularization, and stroke) was observed with long-term use of an ACE-I (ramipril) in moderate-risk patients with CAD, many of whom had preserved LV function, as well as patients at high risk of developing CAD.[16]

**Table 3 Drugs prescribed between 31 and 365 days post-discharge (at least one prescription)**

| | |
|---|---|
| No. of patients | 978 |
| β-Blockers (ATC class C07), *n* (%) | 911 (93.2) |
| Statins (ATC class C10AA), *n* (%) | 867 (88.7) |
| ASA (ATC code B01AC06), *n* (%) | 928 (94.9) |
| Ticlopidin, clopidogrel (ATC codes B01AC04, B01AC05), *n* (%) | 823 (84.2) |
| Antiplatelets (ATC codes B01AC04, B01AC05, B01AC06), *n* (%) | 963 (98.5) |

ATC, anatomical-therapeutic-chemical-classification system; ASA, acetylsalicylic acid.

Similar but smaller benefits were reported in patients with stable coronary artery disease and long-term use of perindopril.[17]

In addition, valsartan was found to be as effective as captopril in post-MI patients presenting with either heart failure or reduced left ventricular systolic function.[18]

Due to this evidence, AMI international guidelines recommend ACE/ARB treatment in acute and long-term phases of AMI in patients who tolerate this class of medications.[14]

However, the clinical impact in the real world of ACE-I/ARB is less known, in part because of variations in drug adherence.[6]

Although it is known that adherence to evidence-based pharmacotherapy predicts better survival, no population outcome study has attempted to differentiate whether these associations are attributable to the drug's biological responsiveness (drug effect) or to the adoption of healthier lifestyles that often accompanies adherent behaviours (healthy-adherer effect).[7]

The methodology adopted in this study—SCSS—virtually eliminated the possibility that our finding was due to confounding related to unaccounted individual characteristics—such as the 'healthy-adherer effect'—unlike most previous literature on the subject.[19]

To our knowledge, this study is the first one focusing on ACE-I/ARB adherence in post-myocardial infarction patients adopting a case-only design, which made it possible to overcome the limitations of previous literature that used interpersonal comparisons. As a consequence, the evidence on the benefit of adhering to prescription medication after a common disease like AMI is reinforced.

The SCSS method cannot produce the same level of evidence as the randomized design, however, like other within-person study-designs, it offers improved control over confounding arising from variables that are constant within an individual. However, it assumes that events arise in a non-homogenous Poisson process, which in turn requires some conditions, already described in Methods. We made every effort to avoid possible bias resulting from failed assumptions. We excluded cardiovascular fatalities and conducted a sensitivity analysis that considered only first events. This came at the cost of a reduced generalizability of our results because they cannot apply to patients with fatal AMI recurrence. However, there is little biological plausibility for a different effect of adherence to ACE-I/ARB in this group of patients.

The assessment of exposure in this study was based on the collection of medication prescriptions. The use of automated pharmacy databases to assess the exposed time to drug therapy is well established in pharmacoepidemiological research.[20] However, it

**Table 4 Results and sensitivity analyses**

| | No. of events during ACE-I/ARB treatment | No. of events during ACE-I/ARB withdrawal | IRR (95% CI) | *P*-value |
|---|---|---|---|---|
| Main analysis ($n = 978$) | 833 | 279 | 0.79 (0.66–0.96) | 0.01 |
| Only first events ($n = 978$) | 725 | 253 | 0.71 (0.59–0.87) | <0.01 |
| Excluding cases with hospitalization >5 days ($n = 236$) | 187 | 59 | 0.38 (0.25–0.58) | <0.01 |
| Excluding cases with AMI in previous 3 years ($n = 945$) | 744 | 272 | 0.79 (0.65–0.96) | 0.01 |

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; IRR, incidence rate ratio; AMI, acute myocardial infarction; CI, confidence interval.

may imply some inevitable inaccuracy, especially when coupled with the SCCS methodology, which is highly sensitive to the definitions of risk periods.[7] First, the collection of a prescription at a pharmacy does not imply its regular consumption. Some patients were probably not taking their prescribed ACE-I/ARB during periods we classified as exposed. This could have caused some bias towards underestimation of the true effect estimate. Second, the DDD, which we used to calculate the number of days covered by ACE-I/ARB is a standard measure, while the actual dosage tailored by the prescribing physician to the individual patient may have been different. This could result in some degree of misclassification of exposed time. The resulting bias would probably be non-differential or towards null, as it would go in opposite directions depending on whether the dosage is higher or lower than DDD.

Finally, small variations in the timing of refills may exist that may be unrelated to adherence. If, during a hospitalization, a patient receives some unrecorded drug supply, some misclassification of exposure is likely to occur, possibly extending to the adjacent period. At the same time, the risk of AMI is likely to change during or soon after hospitalization (e.g. surgery is a known risk factor), causing bias of unpredictable characteristics. We addressed this potential source of bias with a sensitivity analysis that excluded all the patients hospitalized for longer than 5 days. The results of this analysis are reassuring, because the effect estimates were even higher.

Another potential limitation of our study is that we estimated the effect of adherence to ACE-I/ARB only. We cannot exclude the possibility that in periods of non-adherence to ACE-I/ARB, patients were also unexposed to other drugs usually recommended for the secondary prevention of AMI. In this case our risk estimates would be overestimated for specific ACE-I/ARB medication and should be ascribed to some extent to a wider combination of drugs. However, the relative-risk reductions brought about by single drugs are not just additional; for example, a recent study showed that the risk reductions for major cardiovascular events after AMI were 19, 25 and 24% for, respectively, statins, β-blockers, and ACE-inhibitors, but only 36% for the combination of all three.[21]

Similarly, other intrapersonal co-variance of medication adherence with adherence to other risk reducing health behaviours (e.g. physical activity, and smoking cessation) might have overestimated the results. However, this potential bias should be minimized by the presumably longer time required by the latter factors before affecting the risk.

# Conclusions

Our study reports that, within a quite large and homogeneous AMI population, analysed with the self-controlled case-series mythology, adherence to ACE-I/ARB therapy is associated with a significant reduction in long-term AMI recurrence.

**Conflict of interest**: none declared.

## References


1. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso JE, Tracy CM, Woo YJ, Zhao DX, Force CAT. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**127**:529–555.
2. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;**353**:487–497.
3. Shrank WH, Porter ME, Jain SH, Choudhry NK. A blueprint for pharmacy benefit managers to increase value. *Am J Manag Care* 2009;**15**:87–93.
4. Zullig LL, Peterson ED, Bosworth HB. Ingredients of successful interventions to improve medication adherence. *JAMA* 2013;**310**:2611–2612.
5. Bitton A, Choudhry NK, Matlin OS, Swanton K, Shrank WH. The impact of medication adherence on coronary artery disease costs and outcomes: a systematic review. *Am J Med* 2013;**126**:357 e7–357 e27.
6. Dormuth CR, Patrick AR, Shrank WH, Wright JM, Glynn RJ, Sutherland J, Brookhart MA. Statin adherence and risk of accidents: a cautionary tale. *Circulation* 2009;**119**:2051–2057.
7. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006;**25**:1768–1797.
8. Nordmann S, Biard L, Ravaud P, Esposito-Farese M, Tubach F. Case-only designs in pharmacoepidemiology: a systematic review. *PLoS ONE* 2012;**7**:e49444.
9. Di Bartolomeo S, Marino M, Guastaroba P, Valent F, De Palma R. Self-controlled case-series study to verify the effect of adherence to Beta-blockers in secondary prevention of myocardial infarction. *J Am Heart Assoc* 2015;**4**:e001575.
10. Maio V, Marino M, Robeson M, Gagne JJ. Beta-blocker initiation and adherence after hospitalization for acute myocardial infarction. *Eur J Cardiovasc Prev Rehabil* 2011;**18**:438–445.
11. Brauer R, Smeeth L, Anaya-Izquierdo K, Timmis A, Denaxas SC, Farrington CP, Whitaker H, Hemingway H, Douglas I. Antipsychotic drugs and risks of myocardial infarction: a self-controlled case series study. *Eur Heart J* 2015;**36**:984–992.
12. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. *Clin Infect Dis* 2014;**58**:1497–1503.
13. Lonn EM, Yusuf S, Jha P, Montague TJ, Teo KK, Benedict CR, Pitt B. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. *Circulation* 1994;**90**:2056–2069.
14. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr., Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW, American College of Cardiology Foundation/American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**127**:e362–e425.
15. Rutherford JD, Pfeffer MA, Moye LA, Davis BR, Flaker GC, Kowey PR, Lamas GA, Miller HS, Packer M, Rouleau JL, Braunwald E. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. SAVE Investigators. *Circulation* 1994;**90**:1731–1738.
16. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–153.
17. Fox KM, Investigators EUtOrocewPiscAd. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**:782–788.
18. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM, Valsartan in Acute Myocardial Infarction Trial I. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–1906.
19. Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, Krumholz HM, Rumsfeld JS. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med* 2006;**166**:1842–1847.
20. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006;**15**:565–574; discussion 575–7.
21. Choudhry NK, Glynn RJ, Avorn J, Lee JL, Brennan TA, Reisman L, Toscano M, Levin R, Matlin OS, Antman EM, Shrank WH. Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. *Am Heart J* 2014;**167**:51–58 e5.