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Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-042878
Article Type:	Original research
Date Submitted by the Author:	20-Jul-2020
Complete List of Authors:	Soldati, Salvatore ; Department of Epidemiology, Lazio Regional Health Service Di Martino, Mirko; Department of Epidemiology, Lazio Regional Health Service Castagno, Davide; Division of Cardiology, Department of Medical Sciences, University of Turin Davoli, Marina; Department of Epidemiology, Lazio Regional Health Service Fusco, Danilo; Department of Epidemiology, Lazio Regional Health Service
Keywords:	Myocardial infarction < CARDIOLOGY, EPIDEMIOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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In-hospital myocardial infarction and adherence to evidence-based drug therapies: a real-world evaluation

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Key Words: acute myocardial infarction; in-hospital AMI; out-of-hospital AMI; secondary prevention; adherence to poly-therapy.

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ABSTRACT

Background and aims

Little is known about acute myocardial infarction (AMI) occurring during hospital stay. Few studies compared the clinical characteristics and outcome of patients suffering in-hospital (IH-AMI) vs. out-of-hospital (OH-AMI). Guidelines for the secondary prevention of AMI recommended the use of combinations of evidence-based (E-B) drugs. However, observational studies reported poor adherence to chronic poly-therapy. The aims of the study are to measure the adherence to poly-therapy after AMI, to identify determinants of adherence to medications and, above all, to investigate the association between setting of AMI onset (IH-AMI vs. OH-AMI) and adherence to poly-therapy. However, the adherence to E-B drugs recommended for secondary prevention has never been investigated according to AMI setting of onset.

Methods

We identified a cohort of patients hospitalized with an incident MI between 2012 and 2016. Patients were classified as IH-AMI or OH-AMI based on present-on-admission codes. Patients were followed-up for 6 months. Adherence to poly-therapy was defined as a medication possession ratio ≥ 0.75 for at least three of the following drugs: antithrombotics, β -blockers, ACEIs/ARBs, statins.

Results

Among the 25,779 patients included (1,044 [4.1%] had an IH-AMI) 60% were adherent to chronic poly-therapy. Female gender, older age, mental disorders, renal disease, asthma and ongoing concomitant treatments were factors associated with poor adherence. By contrast, patients with more severe AMI and those already taking E-B drugs were more likely to be adherent. Strikingly, the setting of AMI onset was strongly associated with the adherence to poly-therapy: IH-AMI patients were less likely to be adherent to E-B medications during their 6-month follow-up as compared to OH-AMI patients (OR=0.54, 95%CI: 0.47-0.62).

Conclusion

Pharmacotherapy is not consistent with clinical guidelines, especially for IH-AMI patients. Moreover, our results identify groups of patients at risk for poor adherence who might benefit from greater medical attention and dedicated health-care interventions.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- International guidelines for the secondary prevention of AMI recommended the use of combinations of evidence-based (E-B) drugs. Post-AMI survival benefit deriving from adherence to guidelines recommended poly-therapy has been clearly shown in literature. However, observational studies highlighted suboptimal use and poor compliance in the general post-AMI population and in specific subset of affected individuals.
- To the best of our knowledge, no population study attempted to determine whether poly-therapy after AMI differed in patients who had a AMI during their hospital stay as compared with those who experienced an out-of-hospital AMI.
- Adherence to drug treatment was estimated on the basis of defined daily doses. Although this is a useful instrument for comparing the results from different studies, misclassification of drug utilization may have occurred.

INTRODUCTION

Most studies investigating acute myocardial infarction (AMI) epidemiology have focused on outpatients. Insights from these observational studies have informed risk factors and optimal treatment of MI, contributing to a progressive reduction in overall mortality and risk of recurrent AMI worldwide [1-2]. Although it is increasingly recognized that AMI can also occur among patients already hospitalized for other medical conditions [3-4] little is known about the incidence, clinical characteristics, and management of patients experiencing in-hospital AMI (IH-AMI).

Regardless of the setting of incidence, evidence-based secondary prevention strategies are based on changes in lifestyle and evidence based drug therapy. With this regard, international guidelines recommend the combined use of drugs belonging to different anatomical therapeutic chemical (ATC) groups including antithrombotic agents, β -blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and statins [5-6].

Post-AMI survival benefit deriving from long-term adherence to guidelines recommended poly-therapy has been clearly shown in literature [7-12]. However, observational studies highlighted suboptimal use and poor compliance in the general post-AMI population and in specific subset of affected individuals [9, 13-15].

Moreover, substantial between-hospital variation in AMI treatment exist. This variability has important consequences on equal and optimal care delivery. Our research hypothesis is that the setting in which AMI develops may significantly impact on recommended therapeutic strategies and adherence to them.

Therefore, the main objectives of this study were: 1) to measure, in a real world scenario, the adherence to chronic poly-therapy following an AMI; 2) to identify determinants of adherence to E-B drugs specifically focusing on the potential association between setting of onset of AMI (i.e. IH-AMI vs. OHAMI).

To the best of our knowledge, no population study attempted to determine whether poly-therapy after AMI differed in patients who had a AMI during their hospital stay as compared with those who experienced an out-of-hospital AMI. The identification of this subgroup of patients may be useful for health planning purposes and could contribute to better tailor therapeutic interventions to the special needs of this population.

METHODS

Data sources

Our Department has access to health information systems of the Lazio region of Italy that contain mortality, hospital admission and drug claims data. We collected data from the Regional Hospital Information Systems (HIS), the Regional Admission and Discharge Information System (RAD), the Regional Healthcare Emergency Information System (HEIS), the Mortality Information System and the Regional Drug Dispense Registry (PHARMA).

The HIS is an integrated information system designed to collect clinical and administrative information regarding hospital admissions for each patient discharged from public and private hospitals of the Lazio region. The HIS includes patients' characteristics (single anonymous identifier, gender, date and place of birth, and place of residence); admission and discharge dates; discharge diagnoses (up to 6); procedure codes (up to 6) according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM); hospital admission and discharge ward and a regional code that corresponds to the admitting facility.

Since July 2008 tracking of additional information about hospital discharge record has been activated in the Lazio region thanks to RAD Information System (corporate decision nr. D4118). The ministerial directive of December 2010 establishes "the integration of the HIS with additional mandatory sections for the collection of additional information about hospital discharge data". RAD collects additional information on comorbidities (e.g., time to surgery, the presence of AMI diagnosis code at hospital admission time). This information is useful to characterize the patient's severity at the time of hospitalization or surgery and also it be able to support the regional appropriateness and outcome of the treatments evaluation programs.

The HEIS includes all visits occurred in emergency departments of the Lazio region and collects: patient demographic characteristics, admission information, visit and discharge dates and hours, ICD-9-CM diagnosis at discharge, reported symptoms on arrival, status at discharge (e.g., dead, hospitalized, or discharged at home) and triage score.

Information on drugs reimbursed by the national healthcare system and dispensed by public and private pharmacies or by hospital pharmacies at discharge is available from

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3 the Regional Drug Dispense Registry. The data available on each prescription includes
4 patient's identification number, prescribing physician's number, Anatomical-
5 Therapeutic-Chemical (ATC) code of the drug purchased, number of packs, number of
6 units per pack, dosage, unit cost per pack and prescription date.
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10 Any date of death was obtained from the Mortality Information System (MIS).
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13 Data from different information systems have been integrated using a deterministic
14 record linkage procedure based on unique and anonymous subject identifier. In this
15 way, we created a chronological, demographical, residential, clinical, healthcare-related
16 patient profile.
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20 21 22 23 **Setting and study cohort**

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26 The present observational study was based on the population living in the Lazio region
27 Italy. Using data from the regional HIS, the study included a cohort of all patients
28 discharged from hospitals between 1 January 2012 and 31 December 2016 with a
29 diagnosis of AMI. AMI was defined according to International Classification of
30 Diseases Ninth Revision Clinical Modification (ICD-9-CM) codes 410.xx (first or
31 second diagnosis position). In case of multiple hospital admissions, the first admission
32 during the study period was defined as the index admission. Subsequent hospitalizations
33 for any reason were recorded, and repeated admissions within 2 days of discharge were
34 regarded as one single 'episode of care'.
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42 Classification as to whether AMI occurred in-hospital was based on present-on-
43 admission codes from RAD Information System. Admission code diagnosis was
44 available in more than 98% of patients with AMI. Patients aged 18–100 years at
45 discharge were screened for inclusion in the study.
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50 Only incident cases of AMI were included: patients with hospital admission for AMI or
51 related causes (i.e., percutaneous coronary intervention, bypass or surgery of the heart
52 and great vessels) in the 5 years before index admission were excluded.
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56 Patients who were not registered in the regional health assistance file at time of
57 discharge from hospital were excluded (note that healthcare assistance in Italy is offered
58 to all resident citizens without restrictions). Finally, patients who had an individual
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3 follow-up shorter than 30 days were excluded, to give all patients the chance to achieve
4 clinical stability and to guarantee a minimum observation period of one month for
5 consistently estimate adherence to poly-therapy.
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8 9 **Patient and Public Involvement**

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11 No patient involved.
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13 14 **Patient characteristics**

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16 Patients were characterized according to socio-demographic factors (age, gender),
17 comorbidities that might contraindicate prescription of specific ATC group drugs,
18 previous use of E-B drugs, previous use of other (non E-B) medications, previous
19 hospitalization with a diagnosis of mental disorders (ICD-9-CM codes: 290-319),
20 hospital discharge ward and ST-elevation myocardial infarction (STEMI) as indicator of
21 severity of disease. STEMI patients were identified using ICD-9-CM diagnosis codes
22 410.xx, excluding 410.7x (non-ST-elevation MI) and 410.9x (acute MI, not otherwise
23 specified) in any diagnostic position. The following diseases were assessed by health
24 ticket exemption or during hospitalization or emergency department visit for index
25 admission as well as in the 2 years preceding the beginning of follow-up: asthma (ICD-
26 9-CM diagnosis code 493), renal disease (ICD-9-CM diagnosis codes: 582-588, V42.0,
27 V45.1, V56, ICD-9-CM procedure codes: 38.95, 39.95, 54.98, 55.6), sinoatrial
28 bradycardia (ICD-9-CM diagnosis code 427.8). These clinical conditions might
29 contraindicate drug prescription of specific ATC groups due to potential adverse effects
30 (e.g. β -blockers in patients suffering from asthma).
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43 We used the number of distinct, non E-B drugs, prescribed in the 6 months preceding
44 the beginning of follow-up as a crude measure of ongoing concomitant treatments.
45 Medications with the same first five digits of the ATC code were considered as a group
46 [19].
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51 Moreover, to better define patients' clinical profile, during the 6 months preceding
52 follow-up initiation, information was also collected on the use of all E-B drugs:
53 antithrombotic agents, β -blockers, ACEIs, ARBs and statins.
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60 **Follow-up**

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3 We evaluated medication use ‘immediately’ after the acute event, by analyzing
4 prescription patterns during the 6 months following discharge from the index admission.
5 Follow-up started the same date of hospital discharge of the index episode of AMI. The
6 end of follow-up coincided either with the end of 6-month follow-up, the date of death
7 or with the date of all-cause hospitalization whichever came first. The last ‘censoring’
8 criterion allows one to measure the net impact of the hospital that has discharged the
9 patient on medication adherence without the potential interference of subsequent
10 hospitalizations.
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20 **Definition of exposure and outcome.**

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23 AMI were classified as IH-AMI or OH-AMI according to “present-on-admission” codes
24 retrieved using the Regional Admission and Discharge Information System (RAD)
25 which provides information regarding diagnostic codes (present or absent) at the time of
26 presentation.
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31 The main outcome of the study was adherence to chronic poly-therapy at 6-month
32 follow-up. All drugs in this study were included in the patients’ health care plans and
33 were equally available to all residents, in accordance with the universal health care
34 coverage provided to residents of Italy. Information about prescriptions of
35 antithrombotics (ATC: B01AC06, B01AC04, B01AC05, B01AC22, B01AC24,
36 B01AF01, B01AF02, B01AF03, B01AA03, B01AA07, B01AE07), β -blockers (ATC:
37 C07), ACEI/ARBs (ATC: C09), and statins (ATC: C10AA) were retrieved for all
38 patients. Adherence to medication was measured through the medication possession
39 ratio (MPR), calculated as the number of days of medication supplied during the follow-
40 up on the basis of defined daily doses (DDDs) divided by the number of calendar days
41 in the follow-up. Adherence to individual medications was defined as a $MPR \geq 0.75$.
42 Adherence to chronic poly-therapy was defined as a $MPR \geq 0.75$ for at least three of the
43 four evidence-based drugs [12,13].
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56 **Statistical analysis**

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59 Data are presented as column-wise frequencies and percentages for categorical variables
60 (compared using Pearson chi-squared test) and mean value \pm standard deviation for

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3 continuous variables (compared using Student's t-test). Considering the hierarchical
4 data structure (patients are nested within hospitals), logistic multilevel models were
5 performed to take into account potential intra-class correlation. The variance
6 components were expressed in terms of Median Odds Ratio (MOR), a measure that
7 quantifies the variability between clusters, in this case between different hospitals of
8 discharge [20]. The MOR quantifies the variation between clusters by comparing two
9 persons from two randomly chosen clusters. Consider two persons with the same
10 covariates, chosen randomly from two different clusters. MOR is the median odds ratio
11 between the person of higher propensity and the person of lower propensity [21]. This
12 measure is always equal or greater than 1. MOR equal to 1 indicates no variability
13 between clusters; as the variability between group increases MOR value increases. In a
14 first step, MOR was estimated using an intercept-only model. In a second step, MOR
15 was estimated controlling for patient characteristics, in order to ensure that of the
16 heterogeneity of patients within groups (in terms of age, comorbidities or severity of
17 AMI) did not influence the estimates of variance.
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30 Logistic multilevel models were also applied to identify determinants of adherence to
31 evidence-based drugs, taking into account the correlation within clusters. Determinants
32 of adherence were selected based on a priori knowledge [22-23]: gender and age,
33 discharge ward, ST-elevation AMI, use of evidence-based drugs (i.e., antithrombotics,
34 β -blockers, ACEI/ARBs, statins) during the 6 months prior to the index admission
35 (defined as at least one prescription), ongoing concomitant treatments (i.e., number of
36 distinct non-evidence-based drugs) and relevant comorbidities retrieved from the
37 hospital records for both the index admission and the two previous years.
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44 Results were expressed as odds ratios (OR), 95% confidence intervals (95% CI) and p-
45 values. Statistical analyses were carried out using Stata software, version 15
46 (StataCorp.2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp
47 LP).
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RESULTS

The study cohort

The flow chart in figure 1 shows the selection process of the study cohort. Of the 34,854 patients discharged from hospital with a first diagnosis of AMI between January 1st 2012 and December 31th 2016, 25,779 (74%) met the inclusion criteria and were enrolled in the present study. Mean age was 68 years, 17,138 (66%) were male (Table 1). Overall, 11,108 (43%) of patients suffered an AMI with ST segment elevation and the vast majority of patients 20,207 (78%) was discharged from cardiology wards. More than 65% of patients had at least a prescription of E-B medications (β -blockers, anti-thrombotics, ACEI/ARBs or statins) during the 6 months prior to the index admission. Overall, more than two thirds of patients were receiving concomitant treatments (distinct group of non E-B drugs) at the time of AMI and the prevalence of these treatments showed a parallel increase with age .

Among the entire cohort, 1,044 (4.0%) patients suffered an IH-AMI. They were older, had more comorbidities (e.g. renal disease, asthma and mental disorders) and less frequently had a diagnosis of ST-elevation AMI (31% vs 44%) compared with patients experiencing an OH-AMI. In addition, the use of at least one E-B medication before hospitalisation was greater amongst patients suffering an IH-AMI compared with OH-AMI (78% vs 66%). Patients suffering IH-AMI also showed a higher prevalence of ongoing concomitant treatments (number of distinct non E-B drugs prescribed in the 6 months preceding the beginning of follow-up) and less likely were discharged from cardiology wards (48% vs 80%).

Post-AMI adherence to evidence-based medications

The adherence to E-B medications by gender and age group is reported in table 2. Statins were characterised by the highest adherence (78%), followed by antithrombotics (69%), ACEI/ARBs (63%) and β -blockers (50%). Lower adherence was observed among women, most notably for statins and antithrombotics (14 and 12 percentage points lower than men, respectively). This gender difference was attenuated as age increased. Older age groups showed lower adherence to all medications. The adherence

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3 to each of the recommended drugs decreased markedly, for both males and females,
4 moving from the age group '75-84' to the group '85+' years.
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7 Overall, 15,440 (60%) patients were adherent to chronic poly-therapy (as per protocol
8 definition) following an AMI. However, only 6,463 (25%) patients were adherent to the
9 full combination of E-B treatments considered in this study. Women were less likely to
10 be treated with a combination of E-B drugs compared with males (51% vs. 64%). This
11 gender difference was less pronounced as age increased (Table 3).
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16 A significant variability in adherence to poly-therapy between different hospital was
17 observed, even after controlling for patients' characteristics (MOR: 1.46; 95% CI: 1.34-
18 1.64; p-value: <0.001, table 4). This variability was also observed when evaluating
19 adherence to poly-therapy only for IH-AMI patients (MOR: 1.60; 95% CI: 1.34-2.12; p-
20 value: 0.019).
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26 Using logistic multilevel model determinants of adherence to chronic poly-therapy were
27 determined (table 6). A lower probability of adherence was observed in women (OR:
28 0.75; 95% CI: 0.71-0.79; p-value: <0.001) and elderly patients. With this regard, the
29 effect of age was not completely linear: with respect to the reference category (age less
30 than 55 years): the probability of adherence increased in the age group '55-64' years
31 (OR: 1.12; 95% CI: 1.03-1.22; p-value: 0.007) but decreased, although not significantly,
32 in the group '65-74' years (OR: 0.98; 95% CI: 0.90-1.07; p-value: 0.618). A significant
33 drop in the probability of adherence was observed in older age groups ('75-84' years
34 OR: 0.67; 95% CI: 0.61-0.73; p-value: <0.001, ≥85 years; OR: 0.40; 95% CI: 0.35-0.44;
35 p-value: <0.001). A similar trend was observed for the ongoing concomitant treatments
36 in the six months before index admission.
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46 In addition, lower adherence to chronic poly-therapy was observed among patients with
47 comorbidities. In contrast, a significantly higher adherence to poly-therapy was
48 observed amongst patients already taking E-B drugs in the 6 months prior index
49 admission (OR: 1.57; 95% CI: 1.47-1.67; p-value: <0.001) and amongst patients
50 suffering from an ST-elevation MI (OR: 1.48; 95% CI: 1.40-1.56; p-value: <0.001).
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56 After adjustment for potential confounders (including age, gender, renal disease,
57 sinoatrial bradycardia, asthma, mental disorders, ST-elevation AMI, ongoing
58 concomitant treatments and E-B drugs use during the 6 months prior to hospitalization)
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3 patients suffering IH-AMI were 46% less likely to be adherent to poly-therapy as
4 compared with OH-AMI patients (OR: 0.54; 95% CI: 0.47-0.62; p-value: <0.001).
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12 DISCUSSION

13 **Incidence and clinical characteristics of patients with an IH-AMI.**

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17 Acute myocardial infarction occurring in patients who have already been admitted to the
18 hospital for other clinical conditions is an entity that has been poorly investigated so far.
19 In this study, amongst all the patients experiencing an AMI between January 1st 2012
20 and December 31th 2016 in Lazio region (see cohort selection in figure 1), the incidence
21 of IH-AMI was 4.0%. Our study has several key findings. First, compared with OH-
22 AMI patients, those suffering an IH-AMI were more often female, older and less likely
23 to be discharged from cardiology wards, possibly reflecting a higher burden of
24 comorbidities. Indeed, IH-AMI patients had more often a history of renal disease,
25 asthma, mental disorders and more frequently were treated with beta-blockers,
26 antithrombotic agents, ACE-Is/ARBs or statins in the 6 months prior the index event
27 Interestingly, IH-AMI patients less frequently suffered from a ST-elevation AMI. These
28 findings are concordant with the observations from other studies Zahn et al. [24].
29 Maynard et al. [3] reported that patients who had a AMI while hospitalized for other
30 medical conditions were older, more likely to have atypical symptoms, and had higher
31 rates of renal disease, cerebrovascular disease, congestive heart failure, diabetes
32 mellitus, chronic obstructive pulmonary disease, dementia, and cancer than patients who
33 presented as OH-AMI to the Department of Veterans Affairs Health System.
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48 Second, and possibly even more important, we observed that patients experiencing an
49 IH-AMI were less likely to be adherent to E-B medications for secondary prevention of
50 AMI during 6-month follow-up. This may be mainly explained by different patient
51 characteristics. Another possible explanation is that, given the often complex and
52 atypical presentations of cardiac disease in patients with other significant comorbidities.
53 Moreover IH-AMI patients were more likely to be discharged from non-cardiological
54 wards and this may have negatively impacted on the quality of care after the acute
55 event.
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Adherence to chronic poly-therapy.

Concerning the whole study period, we found that after a hospital discharge for AMI, only 60% of patients were adherent to poly-therapy in the following 6 months. Treatments with proven benefit in secondary prevention following an AMI were underused in this study. This result is alarming if we consider that our definition of adherence was not very restrictive (i.e. adherence defined as MPR \geq 75% for at least three of the four predefined E-B drugs) and that adherence was evaluated only for the first 6 months after AMI (adherence should be greater in the initial stages of care and may decrease over time) [25]. Our findings are consistent with the results of other investigations, which reported unsatisfactory prescribing rates of E-B therapies after AMI during different time frames [14] and in different countries [21-22-24].

To the best of our knowledge our study was the first to assess, whether adherence differed between patients who had an IH-AMI as compared with those who experienced an OH-AMI. Interestingly, the setting of AMI onset had a significant impact on poly-therapy adherence. In fact, patients who had an AMI during their hospital stay were less likely to be adherent to chronic poly-therapy compared with patients who had an AMI outside of the hospital. In crude logistic multilevel model, IH-AMI patients were 53% less likely to be adherent as compared with OH-AMI patients (OR: 0.47; 95% CI: 0.41-0.54; p-value: <0.001). After adjustment for potential confounders, this relationship was only slightly attenuated but remained strongly significant (OR: 0.54; 95% CI: 0.47-0.62; p-value: <0.001) (table 6). Of note, estimates were adjusted for all variables identified as determinants of adherence to poly-therapy such as age, gender, renal disease, sinoatrial bradycardia, asthma, mental disorders, ST-elevation MI, ongoing concomitant treatments and E-B drugs use during the 6 months prior to hospitalisation. Although being discharge from a specialized hospital ward (e.g., cardiology, cardiac surgery, coronary care units) was found to be associated with higher adherence rates in previous studies [16-18], we decided not to adjust for discharge ward because we felt it could be a proxy for setting of MI onset. IH-AMI patients were less likely discharged from cardiology wards (48% vs 80%) and this reflects a different care pathway for those compared to patients who had an OH-AMI. In this situation, an adjustment for discharge ward, could have introduced (rather than eliminated) a bias (overadjustment) [27].

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3 We also found that female gender, older age, mental disorders, renal disease, asthma
4 and ongoing concomitant treatments were significantly associated with non-adherence
5 to chronic poly-therapy. Conversely, adherence was positively and significantly
6 associated with patients who had a severe form of disease (ST-elevation AMI) and
7 patients who have already begun E-B drugs in the 6 months before index admission.
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12 Our findings are consistent with the results of other investigations. It is notable that the
13 current study demonstrates that women are receiving less optimal medical therapy in all
14 age groups and all drug categories. The clinical relevance of gender differences varies
15 by age and type of medication. For example, small differences are observed in the use
16 of beta-blockers, larger differences are observed in the use of statins. Additionally,
17 women are still considered at lower risk of acute myocardial infarction, which makes
18 physicians less aware of the risk of new cardiovascular events, causing lower medical
19 adherence. Smolina et al. confirmed these gender differences and showed that treatment
20 was less often initiated in women [28]. Older age was also found to be associated with
21 lower adherence in several previous studies [9,15,17,18]. A higher prevalence of
22 cognitive disorders, memory impairment, and limited ability to absorb new information
23 in the elderly population have been associated with lower adherence. Tuppin et al.
24 reported that adherence to E-B treatment was decreased significantly by an age greater
25 than 74 years [18], confirming our findings. The prescription of complex regimens
26 including multiple drugs has been widely acknowledged as a barrier to patient
27 adherence [29]: the longer the list of drugs prescribed, the lower the adherence of
28 patients. Chronic conditions like asthma, sinoatrial bradycardia and renal disease reduce
29 drug prescription of specific ATC groups due to adverse effects and contraindications
30 increasing the probability of poor adherence to chronic poly-therapy. A previous
31 hospitalization with a diagnosis of mental disorders decreased the odds of adherence:
32 the mechanisms by which mental disorders can affect adherence may include poor
33 motivation, pessimism about treatment effectiveness, diminished attention, memory and
34 cognition, decreased self-care, and even intentional self-harm [30]. Moreover, patients
35 suffering from a ST-elevation AMI or those who had already begun E-B drugs before
36 index AMI were more likely to be adherent to chronic poly-therapy. The former have
37 had a more severe form of the disease and were probably more carefully monitored and
38 made aware of the long-term benefits generated by a continuous and persistent drug
39 treatment. The latter were already used to the chronic and continuous intake of those
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3 drugs that are recommended for the secondary prevention of MI, as a sort of “inertial
4 effect”.
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10 **Strengths and limitations of the study.**

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12 The population-based design, a large number of patients involved and the opportunity to
13 integrate many sources of data to define and analyse the patient’s care pathway are the
14 main strengths of this study. Moreover, to our knowledge, this is the first study to
15 evaluate the adherence to E-B medications, taking into account the setting of AMI
16 onset.
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22 However, the results come from a single region in Italy and may not be generalizable to
23 the other Italian regions due to possible differences in the organization of regional
24 health care services. This notwithstanding, our results are in line with results of similar
25 studies carried out in Italy [31]. Moreover, our pharmaceutical database does not
26 contain information on the prescribed daily doses and adherence to drug treatment was
27 estimated on the basis of the DDDs. Although this is a useful instrument for comparing
28 the results from different studies [32], misclassification of drug utilization may have
29 occurred.
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37 Finally, although all available potential confounders were included in the models to
38 adjust for differences in patients characteristics, we cannot exclude that the lack of more
39 detailed clinical data might have caused unmeasured confounding. We tried to
40 counteract this limit by applying a number of restrictions to obtain a cohort with
41 patients that were as homogeneous as possible.
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48 **Conclusions.**

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51 The availability of information systems offers the opportunity to monitor the quality of
52 care and identify weaknesses in public health-care systems. Although most attention has
53 been paid to patients with AMI admitted via the community emergency medical system
54 or through the emergency department, AMI occurring during hospitalization for other
55 medical problems is an important clinical problem.
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3 Our findings show that, in clinical practice, pharmacotherapy for secondary prevention
4 of AMI is not fully consistent with clinical guidelines, especially for IH-AMI patients.
5 Moreover, we found the setting of AMI onset was strongly associated with adherence to
6 chronic poly-therapy. The results of our study may be of help to identify groups of
7 patients at risk for non-adherence who might benefit from greater medical attention and
8 dedicated health-care interventions.
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14 Finally, our results suggest that efforts to improve adherence to E-B medications in
15 clinical practice, should focus especially on patients who had an infarction during their
16 stay in hospital, an issue that deserves further analysis.
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Figure 1. Cohort selection. Exclusion criteria flow chart

For peer review only

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Table 1. Baseline characteristics of the study cohort

	Total cohort 25.779 (100%)	IH-AMI 1.044 (4.0%)	OH-AMI 24.735 (96.0%)
	N (%)	N (%)	N (%)
Age group (years)			
18-54	4702 (18.24)	101 (9.67)	4601 (18.6)
55-64	5886 (22.83)	149 (14.27)	5737 (23.19)
65-74	6387 (24.78)	243 (23.28)	6144 (24.84)
75-84	6122 (23.75)	360 (34.48)	5762 (23.29)
85 +	2682 (10.4)	191 (18.3)	2491 (10.07)
Age, mean(std), years	67.61 (13.20)	73.19 (12.52)	67.37 (13.18)
Gender (men)	17138 (66.48)	590 (56.51)	16548 (66.9)
ST-elevation MI	11108 (43.09)	319 (30.56)	10789 (43.62)
Renal disease	2335 (9.06)	166 (15.9)	2169 (8.77)
Sinoatrial bradycardia	249 (0.97)	10 (0.96)	239 (0.97)
Asthma	188 (0.73)	12 (1.15)	176 (0.71)
Mental disorders	1098 (4.26)	97 (9.29)	1001 (4.05)
Ongoing concomitant treatments (distinct group of drugs)*			
0-1	7587 (29.43)	180 (17.24)	7407 (29.95)
2-4	8507 (33)	293 (28.07)	8214 (33.21)
5-7	5236 (20.31)	272 (26.05)	4964 (20.07)
8-10	2688 (10.43)	161 (15.42)	2527 (10.22)
>10	1761 (6.83)	138 (13.22)	1623 (6.56)
E-B drugs use (at least 1 prescription)*	17083 (66.27)	811 (77.68)	16272 (65.79)
Discharge ward (cardiology)	20207 (78.39)	501 (47.99)	19706 (79.67)

*, prescribed in the 6 months preceding the index admission; E-B, evidence-based

Table 2. Adherence to evidence-based medications by gender and age group

Age group (years)	β -Blockers (%)	ACEI/ARBs (%)	Antithrombotics (%)	Statins (%)
Males				
18-54	55.20	62.50	77.18	87.74
55-64	54.41	68.83	78.00	88.37
65-74	51.44	68.64	74.20	83.74
75-84	45.18	61.81	65.80	73.83
85 +	37.44	50.25	54.99	58.93
Total	51.10	64.94	73.20	82.59
Females				
18-54	48.95	49.20	66.83	76.33
55-64	51.67	61.61	68.83	78.97
65-74	52.00	65.37	65.27	76.24
75-84	48.92	61.77	58.74	67.44
85 +	40.21	53.99	51.69	51.15
Total	48.34	59.90	61.03	68.81
Whole cohort				
18-54	54.13	60.21	75.39	85.77
55-64	53.84	67.33	75.99	86.41
65-74	51.62	67.59	71.33	81.34
75-84	46.93	61.79	62.50	70.84
85 +	39.19	52.61	52.91	54.03
Total	50.18	63.25	69.12	77.97

ACEI/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Table 3. Adherence to chronic poly-therapy by gender and age group

Age group (years)	Adherence (%) (MPR \geq 75% at least 3 of 4 E-B drugs)	Adherence (%) (MPR \geq 75% for all 4 E-B drugs)
Males		
18-54	67.95	32.20
55-64	70.53	32.47
65-74	67.12	27.72
75-84	54.05	20.12
85 +	39.15	11.81
Total	64.13	27.66
Females		
18-54	51.91	23.55
55-64	60.64	25.67
65-74	58.88	24.59
75-84	51.08	18.06
85 +	36.37	11.53
Total	51.49	19.93
Whole cohort		
18-54	65.19	30.71
55-64	68.47	31.06
65-74	64.47	26.71
75-84	52.66	19.16
85 +	37.40	11.63
Total	59.89	25.07

Table 4. Variation between clusters: the MORs

Multilevel model	Level of analysis	Explanatory variables	MOR (95% CI)	p Value
Two-level regression	(Patients) - HoD	Intercept only	1.86 (1.63 - 2.20)	<0.001
Two-level regression	(Patients) - HoD	Patient's characteristics	1.46 (1.34 - 1.64)	<0.001

HoD, hospital of discharge; MOR, median odds ratio

Table 5. Variation between clusters for in-hospital patients: the MORs

Multilevel model	Level of analysis	Explanatory variables	MOR (95% CI)	p Value
Two-level regression	(Patients) - HoD	Intercept only	1.72 (1.45 - 2.22)	0.005
Two-level regression	(Patients) - HoD	Patient's characteristics	1.60 (1.34 - 2.12)	0.019

HoD, hospital of discharge; MOR, median odds ratio

Table 6. Association between adherence to chronic poly-therapy and symptom onset (IH-AMI VS OH-AMI), socio-demographics and clinical characteristics.

Category	Subcategory	OR	95% CI	p Value
Symptom onset of AMI	OH-AMI	1.00	-	-
	IH-AMI	0.54	0.47 - 0.62	<0.001
Gender of patient	Male	1.00	-	-
	Female	0.75	0.71 - 0.79	<0.001
Age group (years)	(18-54)	1.00	-	-
	(55-64)	1.12	1.03 - 1.22	0.007
	(65-74)	0.98	0.90 - 1.07	0.618
	(75-84)	0.67	0.61 - 0.73	<0.001
	(85 +)	0.40	0.35 - 0.44	<0.001
Renal disease	No	1.00	-	-
	Yes	0.58	0.53 - 0.64	<0.001
Sinoatrial bradycardia	No	1.00	-	-
	Yes	0.83	0.64 - 1.08	0.171
Asthma	No	1.00	-	-
	Yes	0.51	0.37 - 0.69	<0.001
ST-elevation MI	No	1.00	-	-
	Yes	1.48	1.40 - 1.56	<0.001
Ongoing concomitant treatments in the 6 months before index admission (number of distinct group of drugs)	(0-1)	1.00	-	-
	(2-4)	1.05	0.98 - 1.13	0.147
	(5-7)	0.92	0.84 - 1.00	0.055
	(8-10)	0.90	0.81 - 0.99	0.046
	(10 +)	0.73	0.64 - 0.82	<0.001
E-B drugs use in the 6 months before index admission (at least 1 prescription)	No	1.00	-	-
	Yes	1.57	1.47 - 1.67	<0.001
Mental disorders	No	1.00	-	-
	Yes	0.72	0.63 - 0.82	<0.001

OR, odds ratio; CI, confidence interval; E-B, evidence-based

CONTRIBUTORSHIP STATEMENT

Salvatore Soldati contributed to the concept and design of the study, the acquisition of data from the Lazio regional health information systems, the analysis of data and the statistical methodology required for the analytic modelling, the interpretation of results, and the writing of the article.

Mirko Di Martino contributed to the design of the study, the statistical methodology required for the analytic modelling, the interpretation of results, and the writing of the article.

Davide Castagno contributed to the clinical interpretation of results, and the writing of the article.

Marina Davoli and *Daniilo Fusco* contributed to the design of the study, and the critical revision of the paper for important intellectual content, and they have given their final approval of the version submitted for publication.

All authors agree to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

FUNDING STATEMENT

The authors received no specific funding for this research from any funding agency in the public, commercial or not-for-profit sectors.

DATA SHARING STATEMENT

No additional data are available.

PRIVACY LAWS

This study was carried out in full compliance with the current privacy laws. The Department of Epidemiology is legitimized by the Lazio Region Committee in managing and analyzing data from the regional health information systems for epidemiological purposes.

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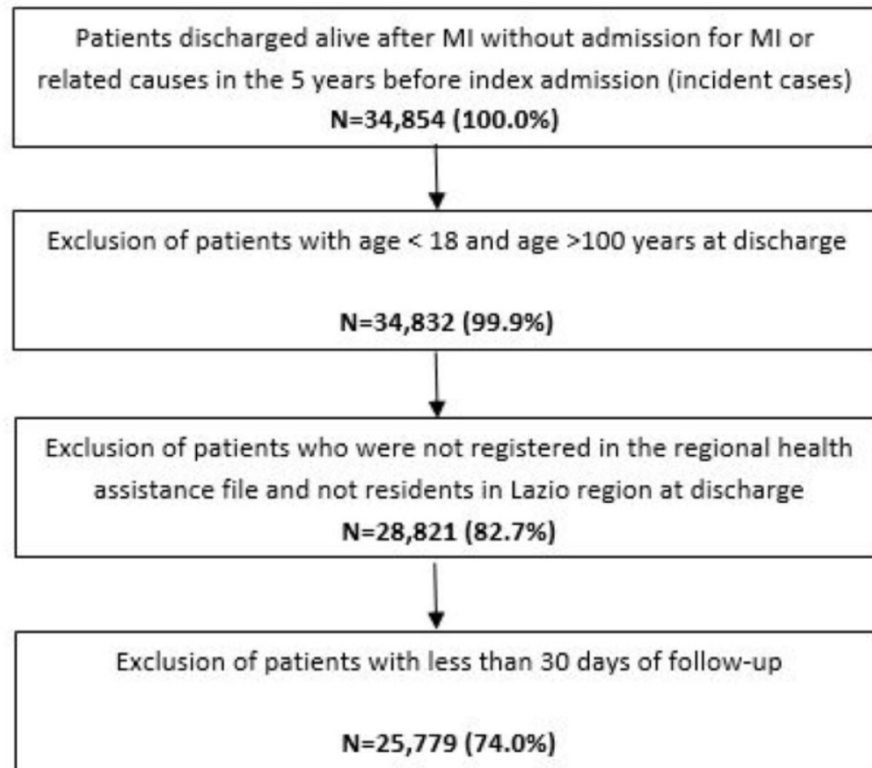


Figure1. Cohort selection. Exclusion criteria flow chart

111x92mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5, 6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6, 7, 8
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5, 6, 7, 8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	We used a multilevel approach. Matching was Not Applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5, 6, 7, 8, 9
Bias	9	Describe any efforts to address potential sources of bias	8, 9,13
Study size	10	Explain how the study size was arrived at	6, 10, 17
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8, 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8, 9
		(b) Describe any methods used to examine subgroups and interactions	The quantitative analysis of the

			interaction between the different levels of the healthcare system was described on pages 8 and 9.
		(c) Explain how missing data were addressed	Not Applicable. We have no missing data.
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	5, 6,7
		(e) Describe any sensitivity analyses	Not Applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, 17
		(b) Give reasons for non-participation at each stage	6, 7
		(c) Consider use of a flow diagram	17
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	(6, 7, 8), 10, 11, 18
		(b) Indicate number of participants with missing data for each variable of interest	Not Applicable. We have no missing data.
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	8, 10, 19, 20, 22
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Not Applicable
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10, 11, 12, 13, 18, 19, 21, 22
		(b) Report category boundaries when continuous variables were categorized	9, 10, 13, 18, 19, 20
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	This is a multilevel study on variation in adherence to clinical guidelines. Therefore the “reporting

			method” suggested by the checklist (i.e. absolute risk measures) might probably be misleading within this framework.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, 11, 12, 19, 20, 21
Discussion			
Key results	18	Summarise key results with reference to study objectives	12, 13, 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13, 14, 15, 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23 The authors received no specific funding for this research from any funding agency in the public, commercial or not-for-profit sectors

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

In-hospital myocardial infarction and adherence to evidence-based drug therapies: a real-world evaluation

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-042878.R1
Article Type:	Original research
Date Submitted by the Author:	04-Nov-2020
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice, Health services research, Public health
Keywords:	Myocardial infarction < CARDIOLOGY, EPIDEMIOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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In-hospital myocardial infarction and adherence to evidence-based drug therapies: a real-world evaluation

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Key Words: acute myocardial infarction; in-hospital AMI; out-of-hospital AMI; secondary prevention; adherence to poly-therapy.

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ABSTRACT

Objectives This study aimed to measure adherence to chronic poly-therapy following an acute myocardial infarction (AMI) and to find out associations between adherence and the setting of AMI onset (In versus Out of hospital) as well as other determinants.

Design Retrospective follow-up study.

Setting Population living in the Lazio Region, Italy.

Participants This study included 25 779 hospitalized patients with a first diagnosis of AMI in 2012-2016, after the exclusion of those with hospital admission for AMI or related causes in the previous five years.

Primary and secondary outcome measures Patients were classified as IH-AMI or OH-AMI according to present-on-admission codes. Adherence was measured based on prescription claims during a 6-month follow-up after hospital discharge, using medication possession ratio (MPR). Adherence to chronic poly-therapy was defined as $MPR \geq 75\%$ to at least 3 of the following medications: antithrombotics, betablockers, ACE inhibitors/angiotensin receptor blockers (ARB) and statins.

Results Among the entire cohort, 1 044 (4%) patients suffered an IH-AMI. Overall, 15 440 (60%) patients were deemed adherent to chronic poly-therapy. Female gender, older age, mental disorders, renal disease, asthma, and ongoing concomitant treatments were factors associated with poor adherence. By contrast, patients with more severe AMI and those already taking evidence-based (E-B) drugs were more likely to be adherent. A strong association between the setting of AMI onset and adherence was observed: IH-AMI patients were 46% less likely to be adherent to E-B medications during their 6-month follow-up as compared to OH-AMI patients (OR=0.54; 95%CI: 0.47-0.62; p-value: <0.001).

Conclusion Pharmacotherapy is not consistent with clinical guidelines, especially for IH-AMI patients. Our findings provide evidence on a previously unidentified groups of patients at risk for poor adherence, who might benefit from greater medical attention and dedicated health-care interventions.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The population-based design, many patients involved and the integration of health information systems to define and analyse the patient's care pathway.
- This is the first study evaluating the adherence to chronic poly-therapy post AMI, taking into account, the setting of AMI onset (In versus Out of hospital).
- This study uses multilevel modelling techniques to control for any variability on medication adherence attributable to hospitals of discharge.
- Misclassification of drug utilization may have occurred because the dosage instructions were not known, and the defined daily doses were used as the dosage assumption.
- Although all available potential confounders were considered to adjust for differences in patients' characteristics, the possibility of unmeasured confounding remains.

INTRODUCTION

Most studies investigating acute myocardial infarction (AMI) epidemiology have target patients with AMI admitted via the community emergency medical system or through the emergency department (OH-AMI). Findings from these observational studies have informed risk factors and optimal treatment of AMI, contributing to a progressive reduction in overall mortality and risk of recurrent AMI worldwide [1-2]. It is increasingly recognized, however, that there are patients whose symptoms onset of AMI begin after being hospitalized for other medical conditions [3-4]. Little is known, in literature, about patients experiencing in-hospital AMI (IH-AMI). One such recent study focused on the incidence, risk factors and mortality-outcomes related to IH-AMI [5].

Regardless of the setting of onset of AMI, evidence-based secondary prevention strategies are based on changes in lifestyle and evidence-based drug therapy. With this regard, international guidelines recommend the combined use of drugs belonging to different anatomical therapeutic chemical (ATC) groups including antithrombotic agents, β -blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and statins [6-7].

Poor medication adherence after AMI is a world-spread problem, which compromises patient outcomes and increases patient mortality. Post-AMI survival benefit deriving from long-term adherence to guidelines recommended poly-therapy has been clearly shown in literature [8-14]. However, observational studies highlighted suboptimal use and poor compliance in the general post-AMI population and in specific subset of affected individuals [11, 14-15].

Moreover, the transition of care from hospital to the community-based setting might also represents an important aspect to be taken into account when assessing medication adherence: patients discharged from a specialized hospital ward (e.g., cardiology, cardiac surgery, coronary care units) were found to be associated with higher adherence rates [14, 16-18]. Typically, the hospital takes care of patients in the “first phase” of follow-up period. After this period, patients are definitively managed by cardiologists in the community-based setting. However, different hospitals have different follow-up protocols, according to the length of follow-up period and frequency of evaluation. These differences in health care delivery generate heterogeneity in the population and raise equity issues in terms of quality and effectiveness of the transition care from the

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3 acute setting to the outpatient setting. For these reasons, our research hypothesis is that
4 the setting in which AMI develops may significantly impact on the probability of being
5 discharge by specialized hospital wards and, consequently, on the recommended
6 therapeutic strategies and adherence to them.
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10 Therefore, the main objectives of this study were: 1) to measure, in a real world
11 scenario, the adherence to chronic poly-therapy following an AMI; 2) to identify
12 determinants of adherence to E-B drugs specifically focusing on the potential
13 association between setting of onset of AMI (i.e. IH-AMI vs. OHAMI).
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18 To the best of our knowledge, no population study attempted to determine whether
19 poly-therapy after AMI differed in patients who had an AMI during their hospital stay
20 as compared with those who experienced an out-of-hospital AMI. The identification of
21 this subgroup of patients may be useful for health planning purposes and could
22 contribute to better tailor therapeutic interventions to the special needs of this
23 population.
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32 **METHODS**

33 **Data sources**

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35 Our Department has access to health information systems of the Lazio region of Italy
36 that contain mortality, hospital admission and drug claims data. We collected data from
37 the Regional Hospital Information Systems (HIS), the Regional Admission and
38 Discharge Information System (RAD), the Regional Healthcare Emergency Information
39 System (HEIS), the Mortality Information System and the Regional Drug Dispense
40 Registry (PHARMA).
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49 The HIS is an integrated information system designed to collect clinical and
50 administrative information regarding hospital admissions for each patient discharged
51 from public and private hospitals of the Lazio region. The HIS includes patients'
52 characteristics (single anonymous identifier, gender, date and place of birth, and place
53 of residence); admission and discharge dates; discharge diagnoses (up to 6); procedure
54 codes (up to 6) according to the International Classification of Disease, Ninth Revision,
55 Clinical Modification (ICD-9-CM); hospital admission and discharge ward and a
56 regional code that corresponds to the admitting facility.
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3 Since July 2008 tracking of additional information about hospital discharge record has
4 been activated in the Lazio region thanks to RAD Information System (corporate
5 decision nr. D4118). The ministerial directive of December 2010 establishes “the
6 integration of the HIS with additional mandatory sections for the collection of
7 additional information about hospital discharge data”. RAD collects additional
8 information on comorbidities (e.g., time to surgery, the presence of AMI diagnosis code
9 at hospital admission time). This information is useful to characterize the severity of
10 patient’s condition at the time of hospitalization or surgery.
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18 The HEIS includes all visits occurred in emergency departments of the Lazio region and
19 collects: patient demographic characteristics, admission information, visit and discharge
20 dates and hours, ICD-9-CM diagnosis at discharge, reported symptoms on arrival, status
21 at discharge (e.g., dead, hospitalized, or discharged at home) and triage score.
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26 Information on drugs reimbursed by the national healthcare system and dispensed by
27 public and private pharmacies or by hospital pharmacies at discharge is available from
28 the Regional Drug Dispense Registry. The data available on each prescription includes
29 patient's identification number, prescribing physician's number, Anatomical-
30 Therapeutic-Chemical (ATC) code of the drug purchased, number of packs, number of
31 units per pack, dosage, unit cost per pack and prescription date.
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37 Any date of death was obtained from the Mortality Information System (MIS).
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40 Data from different information systems have been integrated using a deterministic
41 record linkage procedure based on unique and anonymous subject identifier. In this
42 way, we created a chronological, demographical, residential, clinical, healthcare-related
43 patient profile.
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47 **Setting and study cohort**

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49 The present observational study was based on the population living in the Lazio region,
50 Italy. Using data from the regional HIS, the study included a cohort of all patients
51 discharged from hospitals between 1 January 2012 and 31 December 2016 with a
52 diagnosis of AMI. AMI was defined according to International Classification of
53 Diseases Ninth Revision Clinical Modification (ICD-9-CM) codes 410.xx (first or
54 second diagnosis position). In case of multiple hospital admissions, the first admission
55 during the study period was defined as the index admission. Subsequent hospitalizations
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3 for any reason were recorded, and repeated admissions within 2 days of discharge were
4 regarded as one single ‘episode of care’.
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7 Classification as to whether AMI occurred in-hospital was based on present-on-
8 admission codes from RAD Information System. Admission code diagnosis was
9 available in more than 98% of patients with AMI. Patients aged 18–100 years at
10 discharge were screened for inclusion in the study.
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15 Only incident cases of AMI were included: patients with hospital admission for AMI or
16 related causes (i.e., percutaneous coronary intervention, bypass or surgery of the heart
17 and great vessels) in the 5 years before index admission were excluded.
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21 Patients who were not registered in the regional health assistance file at time of
22 discharge from hospital were excluded (note that healthcare assistance in Italy is offered
23 to all resident citizens without restrictions). Finally, patients who had an individual
24 follow-up shorter than 30 days were excluded, to give all patients the chance to achieve
25 clinical stability and to guarantee a minimum observation period of one month for
26 consistently estimate adherence to poly-therapy.
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31 32 **Patient and Public Involvement**

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35 No patient involved.
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37 38 **Patient characteristics**

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40 Patients were characterized according to socio-demographic factors (age, gender),
41 comorbidities that might contraindicate prescription of specific ATC group drugs,
42 previous use of E-B drugs, previous use of other (non-E-B) medications, previous
43 hospitalization with a diagnosis of mental disorders (ICD-9-CM codes: 290-319),
44 hospital discharge ward and ST-elevation myocardial infarction (STEMI) as indicator of
45 severity of disease. STEMI patients were identified using ICD-9-CM diagnosis codes
46 410.xx, excluding 410.7x (non-ST-elevation AMI) and 410.9x (acute AMI, not
47 otherwise specified) in any diagnostic position. The following diseases were assessed
48 by health ticket exemption or during hospitalization or emergency department visit for
49 index admission as well as in the 2 years preceding the beginning of follow-up: asthma
50 (ICD-9-CM diagnosis code 493), renal disease (ICD-9-CM diagnosis codes: 582-588,
51 V42.0, V45.1, V56, ICD-9-CM procedure codes: 38.95, 39.95, 54.98, 55.6), sinoatrial
52 bradycardia (ICD-9-CM diagnosis code 427.8). These clinical conditions might
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3 contraindicate drug prescription of specific ATC groups due to potential adverse effects
4 (e.g. β -blockers in patients suffering from asthma).
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7 We used the number of distinct, non-E-B drugs, prescribed in the 6 months preceding
8 the beginning of follow-up as a crude measure of ongoing concomitant treatments.
9 Medications with the same first five digits of the ATC code were considered as a group
10 [19].
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14 Moreover, to better define patients' clinical profile, during the 6 months preceding
15 follow-up initiation, information was also collected on the use of all E-B drugs:
16 antithrombotic agents, β -blockers, ACEIs, ARBs and statins.
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20 21 **Follow-up**

22 We evaluated medication use 'immediately' after the acute event, by analyzing
23 prescription patterns during the 6 months following discharge from the index admission.
24 Follow-up started the same date of hospital discharge of the index episode of AMI. The
25 end of follow-up coincided either with the end of 6-month follow-up, the date of death
26 or with the date of all-cause hospitalization whichever came first. The last 'censoring'
27 criterion allows one to measure the net impact of the hospital that has discharged the
28 patient on medication adherence without the potential interference of subsequent
29 hospitalizations.
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37 38 **Definition of exposure and outcome.**

39 AMI were classified as IH-AMI or OH-AMI according to "present-on-admission" codes
40 retrieved using the Regional Admission and Discharge Information System (RAD)
41 which provides information regarding diagnostic codes (present or absent) at the time of
42 hospital presentation.
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48 The main outcome of the study was adherence to chronic poly-therapy at 6-month
49 follow-up. All drugs in this study were included in the patients' health care plans and
50 were equally available to all residents, in accordance with the universal health care
51 coverage provided to residents of Italy. Information about prescriptions of
52 antithrombotics (ATC: B01AC06, B01AC04, B01AC05, B01AC22, B01AC24,
53 B01AF01, B01AF02, B01AF03, B01AA03, B01AA07, B01AE07), β -blockers (ATC:
54 C07), ACEI/ARBs (ATC: C09), and statins (ATC: C10AA) were retrieved for all
55 patients. Adherence to medication was measured through the medication possession
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3 ratio (MPR), calculated as the number of days of medication supplied during the follow-
4 up on the basis of defined daily doses (DDDs) divided by the number of calendar days
5 in the follow-up. Adherence to individual medications was defined as a $MPR \geq 0.75$.
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7 Adherence to chronic poly-therapy was defined as a $MPR \geq 0.75$ for at least three of the
8 four evidence-based drugs [13,14].
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15 **Statistical analysis**

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17 Data are presented as frequencies and percentages for categorical variables and mean
18 value \pm standard deviation for continuous variables. Considering the hierarchical data
19 structure (patients are nested within hospitals), logistic multilevel models were
20 performed to take into account potential intra-class correlation. The variance
21 components were expressed in terms of Median Odds Ratio (MOR), a measure that
22 quantifies the variability between clusters, in this case between different hospitals of
23 discharge. The MOR quantifies the variation between clusters by comparing two
24 persons from two randomly chosen different clusters. Consider two persons with the
25 same covariates, chosen randomly from two different clusters. MOR is the median odds
26 ratio between the person of higher propensity and the person of lower propensity. This
27 measure is always greater than or equal to 1. MOR equal to 1 indicates no variability
28 between clusters, as the variability between group increases MOR value increases [20].
29 In a first step, MOR was estimated using an intercept-only model. In a second step,
30 MOR was estimated controlling for patient characteristics, to ensure that of the
31 heterogeneity of patients within groups (in terms of age, comorbidities, or severity of
32 AMI) did not influence the estimates of variance.
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46 Logistic multilevel models were also applied to identify determinants of adherence to
47 evidence-based drugs, considering the correlation within clusters. Determinants of
48 adherence were selected based on a priori knowledge [21-22]: gender and age,
49 discharge ward, ST-elevation AMI, use of evidence-based drugs (i.e., antithrombotics,
50 β -blockers, ACEI/ARBs, statins) during the 6 months prior to the index admission
51 (defined as at least one prescription), ongoing concomitant treatments (i.e., number of
52 distinct non-evidence-based drugs) and relevant comorbidities retrieved from the
53 hospital records for both the index admission and the two previous years.
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Results were expressed as odds ratios (OR), 95% confidence intervals (95% CI) and p-values. Statistical analyses were carried out using Stata software, version 15 (StataCorp.2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

RESULTS

The study cohort

The flow chart in figure 1 shows the selection process of the study cohort. Of the 34 854 patients discharged from hospital with a first diagnosis of AMI between January 1st 2012 and December 31th 2016, 25 779 (74%) met the inclusion criteria and were enrolled in the present study. Mean age was 68 years, 17 138 (66%) were male (Table 1). Overall, 11 108 (43%) of patients suffered an AMI with ST segment elevation and the largest number of patients 20 207 (78%) was discharged from cardiology wards. More than 65% of patients had at least a prescription of E-B medications (β -blockers, anti-thrombotics, ACEI/ARBs or statins) during the 6 months prior to the index admission. Overall, more than two thirds of patients were receiving concomitant treatments at the time of AMI and the prevalence of these treatments showed a parallel increase with age.

Among the entire cohort, 1 044 (4.0%) patients suffered an IH-AMI. They were older, had more comorbidities (e.g. renal disease, asthma, and mental disorders) and less frequently had a diagnosis of ST-elevation AMI (31% vs. 44%) compared with patients experiencing an OH-AMI. In addition, the use of at least one E-B medication before hospitalisation was greater amongst patients suffering an IH-AMI compared with OH-AMI (78% vs. 66%). Patients suffering IH-AMI also showed a higher prevalence of ongoing concomitant treatments (number of distinct non-E-B drugs prescribed in the 6 months preceding the beginning of follow-up) and less likely were discharged from cardiology wards (48% vs. 80%).

Post-AMI adherence to evidence-based medications

The adherence to E-B medications by gender and age group is reported in table 2. Statins were characterised by the highest adherence (78%), followed by antithrombotics (69%), ACEI/ARBs (63%) and β -blockers (50%). Lower adherence was observed

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3 among women, most notably for statins and antithrombotics (14 and 12 percentage
4 points lower than men, respectively). This gender difference was attenuated as age
5 increased. Older age groups showed lower adherence to all medications. The adherence
6 to each of the recommended drugs decreased markedly, for both males and females,
7 moving from the age group '75-84' to the group '85+' years.
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12 Overall, 15 440 (60%) patients were adherent to chronic poly-therapy (as per protocol
13 definition) following an AMI. However, only 6 463 (25%) patients were adherent to the
14 full combination of E-B treatments considered in this study. Women were less likely to
15 be treated with a combination of E-B drugs compared with males (51% vs. 64%). This
16 gender difference was less pronounced as age increased (Table 3).
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22 A strong variability in adherence to chronic poly-therapy between different hospitals of
23 discharge was observed, even after controlling for patients' characteristics. As reported
24 in table 4 and 5, a higher and statistically significant (p-value: 0.042) variability
25 amongst discharge hospitals was observed for patients suffering IH-AMI (MOR: 1.57;
26 95% CI: 1.33-2.06; p-value: 0.019) as compared with OH-AMI (MOR: 1.46; 95% CI:
27 1.33-1.64; p-value: <0.001).
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33 Using logistic multilevel model, determinants of adherence to chronic poly-therapy
34 were determined (table 6). A lower probability of adherence was observed in women
35 (OR: 0.75; 95% CI: 0.71-0.79; p-value: <0.001) and elderly patients. With this regard,
36 the effect of age was not completely linear: with respect to the reference category (age
37 less than 55 years): the probability of adherence increased in the age group '55-64'
38 years (OR: 1.12; 95% CI: 1.03-1.22; p-value: 0.007) but decreased, although not
39 significantly, in the group '65-74' years (OR: 0.98; 95% CI: 0.90-1.07; p-value: 0.618).
40 A significant drop in the probability of adherence was observed in older age groups
41 ('75-84' years OR: 0.67; 95% CI: 0.61-0.73; p-value: <0.001, ≥ 85 years; OR: 0.40; 95%
42 CI: 0.35-0.44; p-value: <0.001). A similar trend was observed for the ongoing
43 concomitant treatments in the six months before index admission.
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53 In addition, lower adherence to chronic poly-therapy was observed among patients with
54 comorbidities. In contrast, a significantly higher adherence to poly-therapy was
55 observed amongst patients already taking E-B drugs in the 6 months prior index
56 admission (OR: 1.57; 95% CI: 1.47-1.67; p-value: <0.001) and amongst patients
57 suffering from an ST-elevation AMI (OR: 1.48; 95% CI: 1.40-1.56; p-value: <0.001).
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3 Finally, a lower probability of adherence was observed in patients discharged from
4 unspecialized hospital wards as compared with those who discharged from cardiology
5 ward (OR: 0.58; 95% CI: 0.54-0.63; p-value: <0.001).
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9 After adjustment for potential confounders (including age, gender, renal disease,
10 sinoatrial bradycardia, asthma, mental disorders, ST-elevation AMI, ongoing
11 concomitant treatments and E-B drugs use during the 6 months prior to hospitalization)
12 patients suffering IH-AMI were 46% less likely to be adherent to poly-therapy as
13 compared with OH-AMI patients (OR: 0.54; 95% CI: 0.47-0.62; p-value: <0.001).
14 As summarized in table 7, IH-AMI patients showed significantly lower adherence levels
15 for three of four E-B drugs, i.e., statins, antithrombotics and ACEI/ARBs. This “gap”
16 was less significant for Beta-blockers.
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26 DISCUSSION

27 **Prevalence and clinical characteristics of patients with an IH-AMI.**

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29 Acute myocardial infarction occurring in patients who have already been admitted to the
30 hospital for other clinical conditions is an entity that has been poorly investigated so far.
31 In this study, amongst all the patients experiencing an AMI between January 1st 2012
32 and December 31th 2016 in Lazio region (see cohort selection in figure 1), the
33 proportion of patients with IH-AMI of all patients with AMI was 4.0%. Our study has
34 several key findings. First, compared with OH-AMI patients, those suffering an IH-
35 AMI were more often female, older, and less likely to be discharged from cardiology
36 wards, possibly reflecting a higher burden of comorbidities. Indeed, IH-AMI patients
37 had more often a history of renal disease, asthma, mental disorders and more frequently
38 were treated with beta-blockers, antithrombotic agents, ACE-Is/ARBs or statins in the 6
39 months prior the index event Interestingly, IH-AMI patients less frequently suffered
40 from a ST-elevation AMI. Much of these findings are concordant with the observations
41 from a previous study by Zahn et al. [23]. In addition, Maynard et al. [3] reported that
42 patients who had a AMI while hospitalized for other medical conditions were older,
43 more likely to have atypical symptoms, and had higher rates of renal disease,
44 cerebrovascular disease, congestive heart failure, diabetes mellitus, chronic obstructive
45 pulmonary disease, dementia, and cancer than patients who presented as OH-AMI to the
46 Department of Veterans Affairs Health System.
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3 Second, and possibly even more important, we observed that patients experiencing an
4 IH-AMI were less likely to be adherent to E-B medications for secondary prevention of
5 AMI during 6-month follow-up. Moreover IH-AMI patients were more likely to be
6 discharged from non-cardiological wards and this may have negatively impacted on the
7 quality of care after the acute event.
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10 11 12 **Adherence to chronic poly-therapy.** 13

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15 Concerning the whole study period, we found that after a hospital discharge for AMI,
16 only 60% of patients were deemed adherent to poly-therapy in the following 6 months.
17 Treatments with proven benefit in secondary prevention following an AMI were
18 underused in this study. This result is alarming if we consider that our definition of
19 adherence was not very restrictive (i.e. adherence defined as $MPR \geq 75\%$ for at least
20 three of the four predefined E-B drugs) and that adherence was evaluated only for the
21 first 6 months after AMI (adherence should be greater in the initial stages of care and
22 may decrease over time) [24]. Our findings are consistent with the results of other
23 investigations, which reported unsatisfactory prescribing rates of E-B therapies after
24 AMI during different time frames [15] and in different countries [21,22,25].
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33 To the best of our knowledge our study was the first to assess, whether adherence
34 differed between patients who had an IH-AMI as compared with those who experienced
35 an OH-AMI. Interestingly, the setting of AMI onset had a significant impact on poly-
36 therapy adherence. In fact, patients who had an AMI during their hospital stay were less
37 likely to be adherent to chronic poly-therapy compared with patients who had an AMI
38 outside of the hospital. In crude logistic multilevel model, IH-AMI patients were 53%
39 less likely to be adherent as compared with OH-AMI patients (OR: 0.47; 95% CI: 0.41-
40 0.54; p-value: <0.001). After adjustment for potential confounders, this relationship was
41 only slightly attenuated but remained strongly significant (OR: 0.54; 95% CI: 0.47-0.62;
42 p-value: <0.001). Moreover, we observed a greater variability in terms of adherence to
43 multiple recommended secondary prevention therapies for IH-AMI patients. This
44 finding might reflect the lack of standardized and homogenous clinical care pathways
45 within hospitals of discharge for patients who have suffered an AMI during
46 hospitalization for other medical conditions. Of note, estimates were adjusted for all
47 variables identified as determinants of adherence to poly-therapy such as age, gender,
48 renal disease, sinoatrial bradycardia, asthma, mental disorders, ST-elevation AMI,
49 ongoing concomitant treatments and E-B drugs use during the 6 months prior to
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3 hospitalisation. Although being discharge from a specialized hospital ward (e.g.,
4 cardiology, cardiac surgery, coronary care units) was found to be associated with higher
5 adherence rates, we decided not to adjust for discharge ward because we felt it could be
6 a proxy for setting of AMI onset. IH-AMI patients were less likely discharged from
7 cardiology wards (48% vs 80%) and this reflects a different care pathway for those
8 compared to patients who had an OH-AMI. In this situation, an adjustment for
9 discharge ward, could have introduced (rather than eliminated) a bias (overadjustment)
10 [26].
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18 We also found that female gender, older age, mental disorders, renal disease, asthma,
19 and ongoing concomitant treatments were significantly associated with non-adherence
20 to chronic poly-therapy. Conversely, adherence was positively and significantly
21 associated with patients who had a severe form of disease (ST-elevation AMI) and
22 patients who have already begun E-B drugs in the 6 months before index admission.
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28 Our findings are consistent with the results of other investigations. It is notable that the
29 current study demonstrates that women are receiving less optimal medical therapy in all
30 age groups and all drug categories. The clinical relevance of gender differences varies
31 by age and type of medication. For example, small differences are observed in the use
32 of beta-blockers, larger differences are observed in the use of statins. Smolina et al. [27]
33 confirmed these gender differences and showed that treatment was less often initiated in
34 women. Older age was also found to be associated with lower adherence in several
35 previous studies [15,17,18]. A higher prevalence of cognitive disorders, memory
36 impairment, and limited ability to absorb new information in the elderly population
37 have been associated with lower adherence [28]. Tuppin et al. [18] reported that
38 adherence to E-B treatment was decreased significantly by an age greater than 74 years,
39 confirming our findings. The prescription of complex regimens including multiple drugs
40 has been widely acknowledged as a barrier to patient adherence [29]: the longer the list
41 of drugs prescribed, the lower the adherence of patients. Chronic conditions like asthma,
42 sinoatrial bradycardia and renal disease reduce drug prescription of specific ATC
43 groups due to adverse effects and contraindications increasing the probability of poor
44 adherence to chronic poly-therapy. A previous hospitalization with a diagnosis of
45 mental disorders decreased the odds of adherence: the mechanisms by which mental
46 disorders can affect adherence may include poor motivation, pessimism about treatment
47 effectiveness, diminished attention, memory and cognition, decreased self-care, and
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3 even intentional self-harm [30]. Moreover, patients suffering from a ST-elevation AMI
4 or those who had already begun E-B drugs before index AMI were more likely to be
5 adherent to chronic poly-therapy. The former have had a more severe form of the
6 disease and were probably more carefully monitored and made aware of the long-term
7 benefits generated by a continuous and persistent drug treatment. The latter were
8 already used to the chronic and continuous intake of those drugs that are recommended
9 for the secondary prevention of AMI, as a sort of “inertial effect”.

16 **Strengths and limitations of the study.**

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18 The population-based design, many patients involved and the opportunity to integrate
19 many sources of data to define and analyse the patient’s care pathway are the main
20 strengths of this study. Moreover, to our knowledge, this is the first study to evaluate
21 the adherence to E-B medications, considering the setting of AMI onset.

22
23 However, the results come from a single region in Italy and may not be generalizable to
24 the other Italian regions due to possible differences in the organization of regional
25 health care services. This notwithstanding, our results are in line with results of similar
26 studies carried out in Italy [31]. Moreover, our pharmaceutical database does not
27 contain information on the prescribed daily doses and adherence to drug treatment was
28 estimated on the basis of the DDDs [32]. Using DDDs to calculate drug coverage, we
29 run the risk of not accounting for the real-life dosing of a drug when it is used for other
30 than its principal indication [33]. Therefore, misclassification of drug utilization may
31 have occurred because the dosage instructions were not known, and the defined daily
32 doses were used as the dosage assumption. However, in our study, we tried to overcome
33 this limitation by considering DDDs of betablockers reviewed by a panel of physicians,
34 seeing that in secondary prevention post AMI, DDDs are prescribed at lower dosages
35 than the main therapeutic indication.

36
37 In addition, MPR method does not depend on whether patients take their medication as
38 prescribed but depends on the prescription given by physicians. Although we cannot be
39 sure that patients actually took the drug, collecting their medications from the pharmacy
40 is a reasonable indication of an intention to continue with therapy: nevertheless, the
41 results of adherence based on claims data may be overestimated.

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43 Finally, although all available potential confounders were included in the models to
44 adjust for differences in patients’ characteristics, we cannot exclude that the lack of

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3 more detailed clinical data might have caused unmeasured confounding. We tried to
4 counteract this limit by applying several restrictions to obtain a cohort with patients that
5 were as homogeneous as possible.
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8 9 **Conclusions.**

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11 The availability of information systems offers the opportunity to monitor the quality of
12 care and identify weaknesses in public health-care systems. Although most attention has
13 been paid to patients with AMI admitted via the community emergency medical system
14 or through the emergency department, AMI occurring during hospitalization for other
15 medical problems is an important clinical problem.
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19 The results of our study show that, in clinical practice, pharmacotherapy for secondary
20 prevention of AMI is not fully consistent with recommended clinical guidelines,
21 especially for IH-AMI patients. Moreover, a strong association between the setting of
22 AMI onset and adherence to multiple E-B drugs was observed. Our findings provide
23 evidence on a previously unidentified groups of patients at risk for poor adherence, who
24 might benefit from greater medical attention and dedicated health-care interventions.
25 The data strongly support the need for continued efforts to improve adherence to
26 chronic poly-therapy post AMI. These findings could also stimulate efforts to
27 implement hospital strategies to give the same “attention” to IH-AMI patients as OH-
28 AMI patients. In light of the impressive and highly significant impact of the type of
29 discharge ward on the adherence to chronic poly-therapy, it is feasible that much of the
30 “disadvantage” of IH-AMI patients is attributable to the discharge processes, in
31 particular through how far they support effective transitions in and continuity of care. A
32 range of policy tools could be appropriate to reduce this gap, for example by planning
33 differentiated health care transition interventions according to the setting of AMI onset.
34 However, further studies are needed to confirm this association.
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Figure 1. Cohort selection. Exclusion criteria flow chart

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Table 1. Baseline characteristics of the study cohort

	Total cohort	IH-AMI	OH-AMI
	25.779 (100%)	1.044 (4.0%)	24.735 (96.0%)
	N (%)	N (%)	N (%)
Age group (years)			
18-54	4702 (18.24)	101 (9.67)	4601 (18.6)
55-64	5886 (22.83)	149 (14.27)	5737 (23.19)
65-74	6387 (24.78)	243 (23.28)	6144 (24.84)
75-84	6122 (23.75)	360 (34.48)	5762 (23.29)
85 +	2682 (10.4)	191 (18.3)	2491 (10.07)
Age, mean(std), years	67.61 (13.20)	73.19 (12.52)	67.37 (13.18)
Gender (men)	17138 (66.48)	590 (56.51)	16548 (66.9)
ST-elevation AMI	11108 (43.09)	319 (30.56)	10789 (43.62)
Renal disease	2335 (9.06)	166 (15.9)	2169 (8.77)
Sinoatrial bradycardia	249 (0.97)	10 (0.96)	239 (0.97)
Asthma	188 (0.73)	12 (1.15)	176 (0.71)
Mental disorders	1098 (4.26)	97 (9.29)	1001 (4.05)
Ongoing concomitant treatments (distinct group of drugs) *			
0-1	7587 (29.43)	180 (17.24)	7407 (29.95)
2-4	8507 (33)	293 (28.07)	8214 (33.21)
5-7	5236 (20.31)	272 (26.05)	4964 (20.07)
8-10	2688 (10.43)	161 (15.42)	2527 (10.22)
>10	1761 (6.83)	138 (13.22)	1623 (6.56)
E-B drugs use (at least 1 prescription) *	17083 (66.27)	811 (77.68)	16272 (65.79)
Discharge ward (cardiology)	20207 (78.39)	501 (47.99)	19706 (79.67)

*, prescribed in the 6 months preceding the index admission; E-B, evidence-based

Table 2. Adherence to evidence-based medications by gender and age group

Age group (years)	β -Blockers (%)	ACEI/ARBs (%)	Antithrombotics (%)	Statins (%)
Males				
18-54	55.20	62.50	77.18	87.74
55-64	54.41	68.83	78.00	88.37
65-74	51.44	68.64	74.20	83.74
75-84	45.18	61.81	65.80	73.83
85 +	37.44	50.25	54.99	58.93
Total	51.10	64.94	73.20	82.59
Females				
18-54	48.95	49.20	66.83	76.33
55-64	51.67	61.61	68.83	78.97
65-74	52.00	65.37	65.27	76.24
75-84	48.92	61.77	58.74	67.44
85 +	40.21	53.99	51.69	51.15
Total	48.34	59.90	61.03	68.81
Whole cohort				
18-54	54.13	60.21	75.39	85.77
55-64	53.84	67.33	75.99	86.41
65-74	51.62	67.59	71.33	81.34
75-84	46.93	61.79	62.50	70.84
85 +	39.19	52.61	52.91	54.03
Total	50.18	63.25	69.12	77.97

ACEI/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Table 3. Adherence to chronic poly-therapy by gender and age group

Age group (years)	Adherence (%) (MPR \geq 75% at least 3 of 4 E-B drugs)	Adherence (%) (MPR \geq 75% for all 4 E-B drugs)
Males		
18-54	67.95	32.20
55-64	70.53	32.47
65-74	67.12	27.72
75-84	54.05	20.12
85 +	39.15	11.81
Total	64.13	27.66
Females		
18-54	51.91	23.55
55-64	60.64	25.67
65-74	58.88	24.59
75-84	51.08	18.06
85 +	36.37	11.53
Total	51.49	19.93
Whole cohort		
18-54	65.19	30.71
55-64	68.47	31.06
65-74	64.47	26.71
75-84	52.66	19.16
85 +	37.40	11.63
Total	59.89	25.07

Table 4. Variation between clusters for OH-AMI patients: the MORs

Multilevel model	Level of analysis	Explanatory variables	MOR (95% CI)	p Value
Two-level regression	(Patients) - HoD	Intercept only	1.71 (1.50 - 2.02)	<0.001
Two-level regression	(Patients) - HoD	Patient's characteristics	1.46 (1.33 - 1.64)	<0.001

HoD, hospital of discharge; MOR, median odds ratio

Table 5. Variation between clusters for IH-AMI patients: the MORs

Multilevel model	Level of analysis	Explanatory variables	MOR (95% CI)	p Value
Two-level regression	(Patients) - HoD	Intercept only	1.69 (1.43 - 2.16)	0.005
Two-level regression	(Patients) - HoD	Patient's characteristics	1.57 (1.33 - 2.06)	0.019

HoD, hospital of discharge; MOR, median odds ratio

Table 6. Association between adherence to chronic poly-therapy and symptom onset (IH-AMI VS. OH-AMI), socio-demographics and clinical characteristics.

Category	Subcategory	OR	95% CI	p Value
Symptom onset of AMI	OH-AMI	1.00	-	-
	IH-AMI	0.54	0.47 - 0.62	<0.001
Gender of patient	Male	1.00	-	-
	Female	0.75	0.71 - 0.79	<0.001
Age group (years)	(18-54)	1.00	-	-
	(55-64)	1.12	1.03 - 1.22	0.007
	(65-74)	0.98	0.90 - 1.07	0.618
	(75-84)	0.67	0.61 - 0.73	<0.001
	(85 +)	0.40	0.35 - 0.44	<0.001
Renal disease	No	1.00	-	-
	Yes	0.58	0.53 - 0.64	<0.001
Sinoatrial bradycardia	No	1.00	-	-
	Yes	0.83	0.64 - 1.08	0.171
Asthma	No	1.00	-	-
	Yes	0.51	0.37 - 0.69	<0.001
ST-elevation AMI	No	1.00	-	-
	Yes	1.48	1.40 - 1.56	<0.001
Ongoing concomitant treatments in the 6 months before index admission (number of distinct group of drugs)	(0-1)	1.00	-	-
	(2-4)	1.05	0.98 - 1.13	0.147
	(5-7)	0.92	0.84 - 1.00	0.055
	(8-10)	0.90	0.81 - 0.99	0.046
	(10 +)	0.73	0.64 - 0.82	<0.001
E-B drugs use in the 6 months before index admission (at least 1 prescription)	No	1.00	-	-
	Yes	1.57	1.47 - 1.67	<0.001
Mental disorders	No	1.00	-	-
	Yes	0.72	0.63 - 0.82	<0.001

OR, odds ratio; CI, confidence interval; E-B, evidence-based

Table 7. Adherence to evidence-based medications by the setting of AMI onset

Symptom onset of AMI	β -Blockers (%)	ACEI/ARBs (%)	Antithrombotics (%)	Statins (%)
OH-AMI	50.24	63.85	69.88	78.78
IH-AMI	48.66	48.95	51.15	58.72
Whole cohort	50.18	63.25	69.12	77.97

ACEI/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

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CONTRIBUTORSHIP STATEMENT

Salvatore Soldati contributed to the concept and design of the study, the acquisition of data from the Lazio regional health information systems, the analysis of data and the statistical methodology required for the analytic modelling, the interpretation of results, and the writing of the article.

Mirko Di Martino contributed to the design of the study, the statistical methodology required for the analytic modelling, the interpretation of results, and the writing of the article.

Davide Castagno contributed to the clinical interpretation of results, and the writing of the article.

Marina Davoli and *Daniilo Fusco* contributed to the design of the study, and the critical revision of the paper for important intellectual content, and they have given their final approval of the version submitted for publication.

All authors agree to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

COMPETING INTERESTS

The authors declare that they have non-financial associations that may be relevant to the submitted manuscript.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

DATA SHARING STATEMENT

No additional data are available.

PRIVACY LAWS

This study was carried out in full compliance with the current privacy laws. The Department of Epidemiology is legitimized by the Lazio Region Committee in

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3 managing and analyzing data from the regional health information systems for
4 epidemiological purposes.
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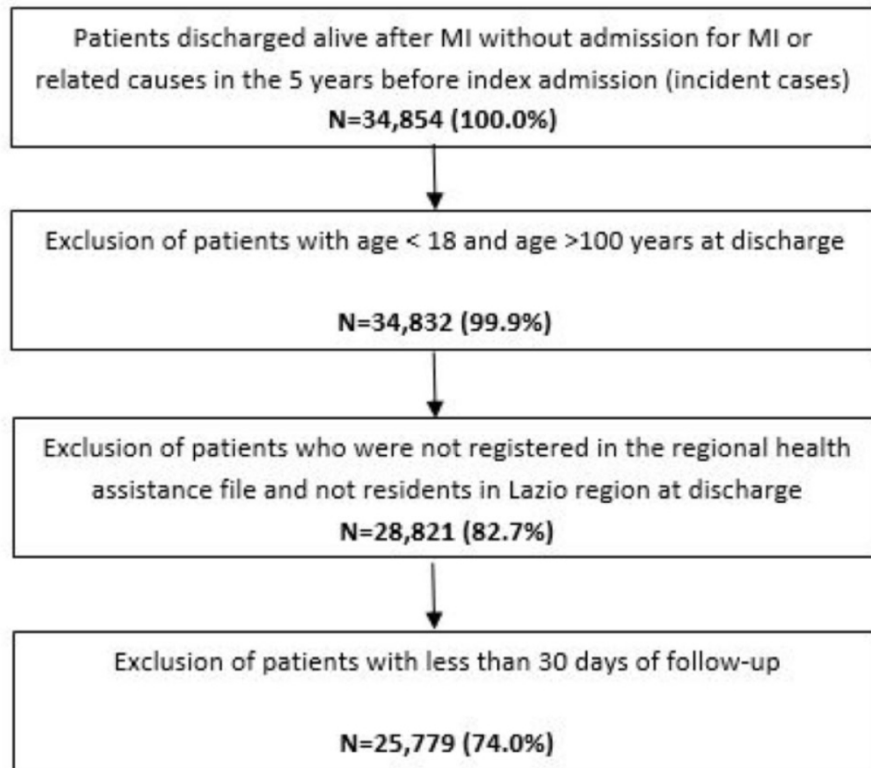


Figure1. Cohort selection. Exclusion criteria flow chart

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4, 5
Methods			
Study design	4	Present key elements of study design early in the paper	5, 6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6, 7, 8
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5, 6, 7, 8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	We used a multilevel approach. Matching was Not Applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8, 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5, 6, 7, 8, 9
Bias	9	Describe any efforts to address potential sources of bias	7, 8, 9, 13
Study size	10	Explain how the study size was arrived at	6, 7, 10, 17
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8, 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9, 10
		(b) Describe any methods used to examine subgroups and interactions	The quantitative analysis of the

			interaction between the different levels of the healthcare system was described on pages 8 and 9.
		(c) Explain how missing data were addressed	Not Applicable. We have no missing data.
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	Not Applicable
		(e) Describe any sensitivity analyses	Not Applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, 11, 12
		(b) Give reasons for non-participation at each stage	10, 17
		(c) Consider use of a flow diagram	10, 17
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 11, 12, 18, 19, 20, 21, 22, 23
		(b) Indicate number of participants with missing data for each variable of interest	Not Applicable. We have no missing data.
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Not Applicable
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10, 11, 12, 21, 23
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Not Applicable
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11, 12, 13, 22, 23
		(b) Report category boundaries when continuous variables were categorized	11, 12, 18, 23
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	This is a multilevel study on variation in adherence to clinical guidelines. Therefore the “reporting

			method” suggested by the checklist (i.e. absolute risk measures) might probably be misleading within this framework.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11, 12, 19, 20, 22
Discussion			
Key results	18	Summarise key results with reference to study objectives	12, 13, 14, 15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15, 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13, 14, 15, 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24 This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

In-hospital myocardial infarction and adherence to evidence-based drug therapies: a real-world evaluation

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-042878.R2
Article Type:	Original research
Date Submitted by the Author:	08-Dec-2020
Complete List of Authors:	Soldati, Salvatore ; Department of Epidemiology, Lazio Regional Health Service Di Martino, Mirko; Department of Epidemiology of the Regional Health Service Lazio Castagno, Davide; Division of Cardiology, Department of Medical Sciences, University of Turin, Turin, Italy Davoli, Marina; Department of Epidemiology, Lazio Regional Health Service Fusco, Danilo; Department of Epidemiology, Lazio Regional Health Service
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice, Health services research, Public health
Keywords:	Myocardial infarction < CARDIOLOGY, EPIDEMIOLOGY, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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In-hospital myocardial infarction and adherence to evidence-based drug therapies: a real-world evaluation

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Key Words: acute myocardial infarction; in-hospital AMI; out-of-hospital AMI; secondary prevention; adherence to poly-therapy.

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ABSTRACT

Objectives This study aimed to measure adherence to chronic poly-therapy following an acute myocardial infarction (AMI) and to find out associations between adherence and the setting of AMI onset (In versus Out of hospital) as well as other determinants.

Design Retrospective follow-up study.

Setting Population living in the Lazio Region, Italy.

Participants This study included 25 779 hospitalized patients with a first diagnosis of AMI in 2012-2016, after the exclusion of those with hospital admission for AMI or related causes in the previous five years.

Primary and secondary outcome measures Patients were classified as IH-AMI or OH-AMI according to present-on-admission codes. Adherence was measured based on prescription claims during a 6-month follow-up after hospital discharge, using medication possession ratio (MPR). Adherence to chronic poly-therapy was defined as $MPR \geq 75\%$ to at least 3 of the following medications: antithrombotics, betablockers, ACE inhibitors/angiotensin receptor blockers (ARB) and statins.

Results Among the entire cohort, 1 044 (4%) patients suffered IH-AMI. Overall, 15 440 (60%) patients were deemed adherent to chronic poly-therapy. Female gender, older age, mental disorders, renal disease, asthma, and ongoing concomitant treatments were factors associated with poor adherence. By contrast, patients with more severe AMI and those already taking evidence-based (E-B) drugs were more likely to be adherent. A strong association between the setting of AMI onset and adherence was observed: IH-AMI patients were 46% less likely to be adherent to E-B medications during their 6-month follow-up as compared to OH-AMI patients (OR=0.54; 95%CI: 0.47-0.62; p-value: <0.001).

Conclusion Pharmacotherapy is not consistent with clinical guidelines, especially for IH-AMI patients. Our findings provide evidence on a previously unidentified groups of patients at risk for poor adherence, who might benefit from greater medical attention and dedicated health-care interventions.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The population-based design, many patients involved and the integration of health information systems to define and analyse the patient's care pathway.
- This is the first study evaluating the adherence to chronic poly-therapy post AMI, taking into account, the setting of AMI onset (In versus Out of hospital).
- This study uses multilevel modelling techniques to control for any variability on medication adherence attributable to hospitals of discharge.
- Misclassification of drug utilization may have occurred because the dosage instructions were not known, and the defined daily doses were used as the dosage assumption.
- Although all available potential confounders were considered to adjust for differences in patients' characteristics, the possibility of unmeasured confounding remains.

INTRODUCTION

Most studies investigating acute myocardial infarction (AMI) epidemiology have target patients with AMI admitted via the community emergency medical system or through the emergency department (OH-AMI). Findings from these observational studies have informed risk factors and optimal treatment of AMI, contributing to a progressive reduction in overall mortality and risk of recurrent AMI worldwide [1-2]. It is increasingly recognized, however, that there are patients whose symptoms onset of AMI begin after being hospitalized for other medical conditions [3-4]. Little is known, in literature, about patients experiencing in-hospital AMI (IH-AMI). One such recent study focused on the incidence, risk factors and mortality-outcomes related to IH-AMI [5].

Regardless of the setting of onset of AMI, evidence-based secondary prevention strategies are based on changes in lifestyle and evidence-based drug therapy. With this regard, international guidelines recommend the combined use of drugs belonging to different anatomical therapeutic chemical (ATC) groups including antithrombotic agents, β -blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and statins [6-7].

Poor medication adherence after AMI is a world-spread problem, which compromises patient outcomes and increases patient mortality. Post-AMI survival benefit deriving from long-term adherence to guidelines recommended poly-therapy has been clearly shown in literature [8-14]. However, observational studies highlighted suboptimal use and poor compliance in the general post-AMI population and in specific subset of affected individuals [11, 14-15].

Moreover, the transition of care from hospital to the community-based setting might also represents an important aspect to be taken into account when assessing medication adherence: patients discharged from a specialized hospital ward (e.g., cardiology, cardiac surgery, coronary care units) were found to be associated with higher adherence rates [14, 16-18]. Typically, the hospital takes care of patients in the “first phase” of follow-up period. After this period, patients are definitively managed by cardiologists in the community-based setting. However, different hospitals have different follow-up protocols, according to the length of follow-up period and frequency of evaluation. These differences in health care delivery generate heterogeneity in the population and raise equity issues in terms of quality and effectiveness of the transition care from the

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3 acute setting to the outpatient setting. For these reasons, our research hypothesis is that
4 the setting in which AMI develops may significantly impact on the probability of being
5 discharge by specialized hospital wards and, consequently, on the recommended
6 therapeutic strategies and adherence to them.
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11 Therefore, the main objectives of this study were: 1) to measure, in a real-world
12 scenario, the adherence to chronic poly-therapy following an AMI; 2) to identify
13 determinants of adherence to E-B drugs specifically focusing on the potential
14 association between setting of onset of AMI (i.e., IH-AMI vs. OHAMI).
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21 **METHODS**

22 **Data sources**

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24 Our Department has access to health information systems of the Lazio region of Italy
25 that contain mortality, hospital admission and drug claims data. We collected data from
26 the Regional Hospital Information Systems (HIS), the Regional Admission and
27 Discharge Information System (RAD), the Regional Healthcare Emergency Information
28 System (HEIS), the Mortality Information System and the Regional Drug Dispense
29 Registry (PHARMA).
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37 The HIS is an integrated information system designed to collect clinical and
38 administrative information regarding hospital admissions for each patient discharged
39 from public and private hospitals of the Lazio region. The HIS includes patients'
40 characteristics (single anonymous identifier, gender, date and place of birth, and place
41 of residence); admission and discharge dates; discharge diagnoses (up to 6); procedure
42 codes (up to 6) according to the International Classification of Disease, Ninth Revision,
43 Clinical Modification (ICD-9-CM); hospital admission and discharge ward and a
44 regional code that corresponds to the admitting facility.
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52 Since July 2008 tracking of additional information about hospital discharge record has
53 been activated in the Lazio region thanks to RAD Information System (corporate
54 decision nr. D4118). The ministerial directive of December 2010 establishes "the
55 integration of the HIS with additional mandatory sections for the collection of
56 additional information about hospital discharge data". RAD collects additional
57 information on comorbidities (e.g., time to surgery, the presence of AMI diagnosis code
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3 at hospital admission time). This information is useful to characterize the severity of
4 patient's condition at the time of hospitalization or surgery. These additional data are
5 inserted into the RAD forms at the time of patient's hospital discharge, when the
6 diagnostic and therapeutic care pathways are clearly defined.
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11 The HEIS includes all visits occurred in emergency departments of the Lazio region and
12 collects patient demographic characteristics, admission information, visit and discharge
13 dates and hours, ICD-9-CM diagnosis at discharge, reported symptoms on arrival, status
14 at discharge (e.g., dead, hospitalized, or discharged at home) and triage score.
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19 Information on drugs reimbursed by the national healthcare system and dispensed by
20 public and private pharmacies or by hospital pharmacies at discharge is available from
21 the Regional Drug Dispense Registry. The data available on each prescription includes
22 patient's identification number, prescribing physician's number, Anatomical-
23 Therapeutic-Chemical (ATC) code of the drug purchased, number of packs, number of
24 units per pack, dosage, unit cost per pack and prescription date.
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30 Any date of death was obtained from the Mortality Information System (MIS).
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33 Data from different information systems have been integrated using a deterministic
34 record linkage procedure based on unique and anonymous subject identifier. In this
35 way, we created a chronological, demographical, residential, clinical, healthcare-related
36 patient profile.
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40 **Setting and study cohort**

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42 The present observational study was based on the population living in the Lazio region,
43 Italy. Using data from the regional HIS, the study included a cohort of all patients
44 discharged from hospitals between 1 January 2012 and 31 December 2016 with a
45 diagnosis of AMI. AMI was defined according to International Classification of
46 Diseases Ninth Revision Clinical Modification (ICD-9-CM) codes 410.xx (first or
47 second diagnosis position). In case of multiple hospital admissions, the first admission
48 during the study period was defined as the index admission. Subsequent hospitalizations
49 for any reason were recorded, and repeated admissions within 2 days of discharge were
50 regarded as one single 'episode of care'.
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60 Classification as to whether AMI occurred in-hospital was based on present-on-
admission codes from RAD Information System, which provides information regarding

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3 diagnostic codes (present, absent, presence cannot be deduced from clinical
4 documentation, not applicable) at the time of hospital presentation. AMI patients with
5 admission code diagnosis (present) were classified as OH-AMI, patients without
6 admission code diagnosis (absent) were classified as IH-AMI. Admission code
7 diagnosis (present or absent) was available in more than 98% of AMI patients. To
8 improve identification of unambiguously IH-onset AMI, we excluded patients with
9 unclear admission code diagnosis (“presence cannot be deduced from clinical
10 documentation” or “not applicable”). In such manner, we should be able to reduce the
11 possible misclassification of exposure due to critical situations, in which patients may
12 have ambiguous diagnosis at the time of hospital admission.
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21 Patients aged 18–100 years at discharge were screened for inclusion in the study. Only
22 incident cases of AMI were included: patients with hospital admission for AMI or
23 related causes (i.e., percutaneous coronary intervention, bypass or surgery of the heart
24 and great vessels) in the 5 years before index admission were excluded.
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29 Patients who were not registered in the regional health assistance file at time of
30 discharge from hospital were excluded (note that healthcare assistance in Italy is offered
31 to all resident citizens without restrictions). Finally, patients who had an individual
32 follow-up shorter than 30 days were excluded, to give all patients the chance to achieve
33 clinical stability and to guarantee a minimum observation period of one month for
34 consistently estimate adherence to poly-therapy.
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40 **Patient and Public Involvement**

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42 No patient involved.
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45 **Patient characteristics**

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47 Patients were characterized according to socio-demographic factors (age, gender),
48 comorbidities that might contraindicate prescription of specific ATC group drugs,
49 previous use of E-B drugs, previous use of other (non-E-B) medications, previous
50 hospitalization with a diagnosis of mental disorders (ICD-9-CM codes: 290-319),
51 hospital discharge ward and ST-elevation myocardial infarction (STEMI) as indicator of
52 severity of disease. STEMI patients were identified using ICD-9-CM diagnosis codes
53 410.xx, excluding 410.7x (non-ST-elevation AMI) and 410.9x (acute AMI, not
54 otherwise specified) in any diagnostic position. The following diseases were assessed
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3 by health ticket exemption or during hospitalization or emergency department visit for
4 index admission as well as in the 2 years preceding the beginning of follow-up: asthma
5 (ICD-9-CM diagnosis code 493), renal disease (ICD-9-CM diagnosis codes: 582-588,
6 V42.0, V45.1, V56, ICD-9-CM procedure codes: 38.95, 39.95, 54.98, 55.6), sinoatrial
7 bradycardia (ICD-9-CM diagnosis code 427.8). These clinical conditions might
8 contraindicate drug prescription of specific ATC groups due to potential adverse effects
9 (e.g., β -blockers in patients suffering from asthma).

10
11 We used the number of distinct, non-E-B drugs, prescribed in the 6 months preceding
12 the beginning of follow-up as a crude measure of ongoing concomitant treatments.
13 Medications with the same first five digits of the ATC code were considered as a group
14 [19].

15
16 Moreover, to better define patients' clinical profile, during the 6 months preceding
17 follow-up initiation, information was also collected on the use of all E-B drugs:
18 antithrombotic agents, β -blockers, ACEIs, ARBs and statins.

19 20 21 22 23 24 25 26 27 28 29 30 31 **Follow-up**

32 We evaluated medication use 'immediately' after the acute event, by analyzing
33 prescription patterns during the 6 months following discharge from the index admission.
34 Follow-up started the same date of hospital discharge of the index episode of AMI. The
35 end of follow-up coincided either with the end of 6-month follow-up, the date of death
36 or with the date of all-cause hospitalization whichever came first. The last 'censoring'
37 criterion allows one to measure the net impact of the hospital that has discharged the
38 patient on medication adherence without the potential interference of subsequent
39 hospitalizations.

40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 **Definition of exposure and outcome.**

AMI were classified as IH-AMI or OH-AMI according to "present-on-admission" codes
retrieved using the Regional Admission and Discharge Information System (RAD)
which provides information regarding diagnostic codes (present or absent) at the time of
hospital presentation.

The main outcome of the study was adherence to chronic poly-therapy at 6-month
follow-up. All drugs in this study were included in the patients' health care plans and
were equally available to all residents, in accordance with the universal health care

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3 coverage provided to residents of Italy. Information about prescriptions of
4 antithrombotics (ATC: B01AC06, B01AC04, B01AC05, B01AC22, B01AC24,
5 B01AF01, B01AF02, B01AF03, B01AA03, B01AA07, B01AE07), β -blockers (ATC:
6 C07), ACEI/ARBs (ATC: C09), and statins (ATC: C10AA) were retrieved for all
7 patients. Adherence to medication was measured through the medication possession
8 ratio (MPR), calculated as the number of days of medication supplied during the follow-
9 up on the basis of defined daily doses (DDDs) divided by the number of calendar days
10 in the follow-up. Adherence to individual medications was defined as a $MPR \geq 0.75$.
11 Adherence to chronic poly-therapy was defined as a $MPR \geq 0.75$ for at least three of the
12 four evidence-based drugs [13,14].
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24 **Statistical analysis**

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26 Data are presented as frequencies and percentages for categorical variables and mean
27 value \pm standard deviation for continuous variables. Considering the hierarchical data
28 structure (patients are nested within hospitals), logistic multilevel models were
29 performed to take into account potential intra-class correlation. The variance
30 components were expressed in terms of Median Odds Ratio (MOR), a measure that
31 quantifies the variability between clusters, in this case between different hospitals of
32 discharge. The MOR quantifies the variation between clusters by comparing two
33 persons from two randomly chosen different clusters. Consider two persons with the
34 same covariates, chosen randomly from two different clusters. MOR is the median odds
35 ratio between the person of higher propensity and the person of lower propensity. This
36 measure is always greater than or equal to 1. MOR equal to 1 indicates no variability
37 between clusters, as the variability between group increases MOR value increases [20].
38 In a first step, MOR was estimated using an intercept-only model. In a second step,
39 MOR was estimated controlling for patient characteristics, to ensure that of the
40 heterogeneity of patients within groups (in terms of age, comorbidities, or severity of
41 AMI) did not influence the estimates of variance.
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55 Logistic multilevel models were also applied to identify determinants of adherence to
56 evidence-based drugs, considering the correlation within clusters. Determinants of
57 adherence were selected based on a priori knowledge [21-22]: gender and age,
58 discharge ward, ST-elevation AMI, use of evidence-based drugs (i.e., antithrombotics,
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3 β -blockers, ACEI/ARBs, statins) during the 6 months prior to the index admission
4 (defined as at least one prescription), ongoing concomitant treatments (i.e., number of
5 distinct non-evidence-based drugs) and relevant comorbidities retrieved from the
6 hospital records for both the index admission and the two previous years.
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11 Results were expressed as odds ratios (OR), 95% confidence intervals (95% CI) and p-
12 values. Statistical analyses were carried out using Stata software, version 15
13 (StataCorp.2015. Stata Statistical Software: Release 15. College Station, TX: StataCorp
14 LP).
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21 RESULTS

22 The study cohort

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26 The flow chart in Figure 1 shows the selection process of the study cohort. Of the 34
27 854 patients discharged from hospital with a first diagnosis of AMI between January 1st
28 2012 and December 31th 2016, 25 779 (74%) met the inclusion criteria and were
29 enrolled in the present study. Mean age was 68 years, 17 138 (66%) were male (Table
30 1). Overall, 11 108 (43%) of patients suffered an AMI with ST segment elevation and
31 the largest number of patients 20 207 (78%) was discharged from cardiology wards.
32 More than 65% of patients had at least a prescription of E-B medications (β -blockers,
33 anti-thrombotics, ACEI/ARBs or statins) during the 6 months prior to the index
34 admission. Overall, more than two thirds of patients were receiving concomitant
35 treatments at the time of AMI and the prevalence of these treatments showed a parallel
36 increase with age.
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46 Among the entire cohort, 1 044 (4.0%) patients suffered an IH-AMI. They were older,
47 had more comorbidities (e.g., renal disease, asthma, and mental disorders) and less
48 frequently had a diagnosis of ST-elevation AMI (31% vs. 44%) compared with patients
49 experiencing an OH-AMI. In addition, the use of at least one E-B medication before
50 hospitalisation was greater amongst patients suffering an IH-AMI compared with OH-
51 AMI (78% vs. 66%). Patients suffering IH-AMI also showed a higher prevalence of
52 ongoing concomitant treatments (number of distinct non-E-B drugs prescribed in the 6
53 months preceding the beginning of follow-up) and less likely were discharged from
54 cardiology wards (48% vs. 80%).
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Post-AMI adherence to evidence-based medications

The adherence to E-B medications by gender and age group is reported in Table 2. Statins were characterised by the highest adherence (78%), followed by antithrombotics (69%), ACEI/ARBs (63%) and β -blockers (50%). Lower adherence was observed among women, most notably for statins and antithrombotics (14 and 12 percentage points lower than men, respectively). This gender difference was attenuated as age increased. Older age groups showed lower adherence to all medications. The adherence to each of the recommended drugs decreased markedly, for both males and females, moving from the age group '75-84' to the group '85+' years.

Overall, 15 440 (60%) patients were adherent to chronic poly-therapy (as per protocol definition) following an AMI. However, only 6 463 (25%) patients were adherent to the full combination of E-B treatments considered in this study. Women were less likely to be treated with a combination of E-B drugs compared with males (51% vs. 64%). This gender difference was less pronounced as age increased (Table 3).

A strong variability in adherence to chronic poly-therapy between different hospitals of discharge was observed, even after controlling for patients' characteristics. As reported in Table 4 and 5, a higher and statistically significant (p-value: 0.042) variability amongst discharge hospitals was observed for patients suffering IH-AMI (MOR: 1.57; 95% CI: 1.33-2.06; p-value: 0.019) as compared with OH-AMI (MOR: 1.46; 95% CI: 1.33-1.64; p-value: <0.001).

Using logistic multilevel model, determinants of adherence to chronic poly-therapy were determined (table 6). A lower probability of adherence was observed in women (OR: 0.75; 95% CI: 0.71-0.79; p-value: <0.001) and elderly patients. With this regard, the effect of age was not completely linear: with respect to the reference category (age less than 55 years): the probability of adherence increased in the age group '55-64' years (OR: 1.12; 95% CI: 1.03-1.22; p-value: 0.007) but decreased, although not significantly, in the group '65-74' years (OR: 0.98; 95% CI: 0.90-1.07; p-value: 0.618). A significant drop in the probability of adherence was observed in older age groups ('75-84' years OR: 0.67; 95% CI: 0.61-0.73; p-value: <0.001, ≥ 85 years; OR: 0.40; 95% CI: 0.35-0.44; p-value: <0.001). A similar trend was observed for the ongoing concomitant treatments in the six months before index admission.

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3 In addition, lower adherence to chronic poly-therapy was observed among patients with
4 comorbidities. In contrast, a significantly higher adherence to poly-therapy was
5 observed amongst patients already taking E-B drugs in the 6 months prior index
6 admission (OR: 1.57; 95% CI: 1.47-1.67; p-value: <0.001) and amongst patients
7 suffering from an ST-elevation AMI (OR: 1.48; 95% CI: 1.40-1.56; p-value: <0.001).
8 Finally, a lower probability of adherence was observed in patients discharged from
9 unspecialized hospital wards as compared with those who discharged from cardiology
10 ward (OR: 0.58; 95% CI: 0.54-0.63; p-value: <0.001).
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17 After adjustment for potential confounders (including age, gender, renal disease,
18 sinoatrial bradycardia, asthma, mental disorders, ST-elevation AMI, ongoing
19 concomitant treatments, and E-B drugs use during the 6 months prior to hospitalization)
20 patients suffering IH-AMI were 46% less likely to be adherent to poly-therapy as
21 compared with OH-AMI patients (OR: 0.54; 95% CI: 0.47-0.62; p-value: <0.001).
22 As summarized in table 7, IH-AMI patients showed significantly lower adherence levels
23 for three of four E-B drugs, i.e., statins, antithrombotics and ACEI/ARBs. This “gap”
24 was less significant for Beta-blockers.
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35 DISCUSSION

36 Prevalence and clinical characteristics of IH-AMI patients.

37 Acute myocardial infarction occurring in patients who have already been admitted to the
38 hospital for other clinical conditions is an entity that has been poorly investigated so far.
39 In this study, amongst all the patients experiencing AMI between January 1st 2012 and
40 December 31th 2016 in Lazio region (see cohort selection in figure 1), the proportion of
41 patients with IH-AMI of all patients with AMI was 4.0%. Our study has several key
42 findings. First, compared with OH-AMI patients, those suffering IH-AMI were more
43 often female, older, and less likely to be discharged from cardiology wards, possibly
44 reflecting a higher burden of comorbidities. Indeed, IH-AMI patients had more often a
45 history of renal disease, asthma, mental disorders and more frequently were treated with
46 beta-blockers, antithrombotic agents, ACE-Is/ARBs or statins in the 6 months prior the
47 index event Interestingly, IH-AMI patients less frequently suffered from ST-elevation
48 AMI. Much of these findings are concordant with the observations from a previous
49 study by Zahn et al. [23]. In addition, Maynard et al. [3] reported that patients who had
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3 AMI while hospitalized for other medical conditions were older, more likely to have
4 atypical symptoms, and had higher rates of renal disease, cerebrovascular disease,
5 congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease,
6 dementia, and cancer than patients who presented as OH-AMI to the Department of
7 Veterans Affairs Health System.
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12 Second, and possibly even more important, we observed that patients experiencing IH-
13 AMI were less likely to be adherent to E-B medications for secondary prevention of
14 AMI during 6-month follow-up. Moreover IH-AMI patients were more likely to be
15 discharged from non-cardiological wards and this may have negatively impacted on the
16 quality of care after the acute event.
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22 **Adherence to chronic poly-therapy.**

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24 Concerning the whole study period, we found that after a hospital discharge for AMI,
25 only 60% of patients were deemed adherent to poly-therapy in the following 6 months.
26 Treatments with proven benefit in secondary prevention following AMI were underused
27 in this study. This result is alarming if we consider that our definition of adherence was
28 not very restrictive (i.e., adherence defined as MPR \geq 75% for at least three of the four
29 predefined E-B drugs) and that adherence was evaluated only for the first 6 months after
30 AMI (adherence should be greater in the initial stages of care and may decrease over
31 time) [24]. Our findings are consistent with the results of other investigations, which
32 reported unsatisfactory prescribing rates of E-B therapies after AMI during different
33 time frames [15] and in different countries [21,22,25].
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43 To the best of our knowledge our study was the first to assess, whether adherence
44 differed between patients who had IH-AMI as compared with those who experienced
45 OH-AMI. Interestingly, the setting of AMI onset had a significant impact on poly-
46 therapy adherence. In fact, patients who had AMI during their hospital stay were less
47 likely to be adherent to chronic poly-therapy compared with patients who had AMI
48 outside of the hospital. In crude logistic multilevel model, IH-AMI patients were 53%
49 less likely to be adherent as compared with OH-AMI patients (OR: 0.47; 95% CI: 0.41-
50 0.54; p-value: <0.001). After adjustment for potential confounders, this relationship was
51 only slightly attenuated but remained strongly significant (OR: 0.54; 95% CI: 0.47-0.62;
52 p-value: <0.001). Moreover, we observed a greater variability in terms of adherence to
53 multiple recommended secondary prevention therapies for IH-AMI patients. This
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3 finding might reflect the lack of standardized and homogenous clinical care pathways
4 within hospitals of discharge for patients who have suffered AMI during hospitalization
5 for other medical conditions. Of note, estimates were adjusted for all variables identified
6 as determinants of adherence to poly-therapy such as age, gender, renal disease,
7 sinoatrial bradycardia, asthma, mental disorders, ST-elevation AMI, ongoing
8 concomitant treatments, and E-B drugs use during the 6 months prior to hospitalisation.
9 Although being discharge from a specialized hospital ward (e.g., cardiology, cardiac
10 surgery, coronary care units) was found to be associated with higher adherence rates, we
11 decided not to adjust for discharge ward because we felt it could be a proxy for setting
12 of AMI onset. IH-AMI patients were less likely discharged from cardiology wards (48%
13 vs 80%) and this reflects a different care pathway for those compared to patients who
14 had OH-AMI. In this situation, an adjustment for discharge ward, could have introduced
15 (rather than eliminated) a bias (overadjustment) [26].
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26 We also found that female gender, older age, mental disorders, renal disease, asthma,
27 and ongoing concomitant treatments were significantly associated with non-adherence
28 to chronic poly-therapy. Conversely, adherence was positively and significantly
29 associated with patients who had a severe form of disease (ST-elevation AMI) and
30 patients who have already begun E-B drugs in the 6 months before index admission.
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36 Our findings are consistent with the results of other investigations. It is notable that the
37 current study demonstrates that women are receiving less optimal medical therapy in all
38 age groups and all drug categories. The clinical relevance of gender differences varies
39 by age and type of medication. For example, small differences are observed in the use
40 of beta-blockers, larger differences are observed in the use of statins. Smolina et al. [27]
41 confirmed these gender differences and showed that treatment was less often initiated in
42 women. Older age was also found to be associated with lower adherence in several
43 previous studies [15,17,18]. A higher prevalence of cognitive disorders, memory
44 impairment, and limited ability to absorb new information in the elderly population
45 have been associated with lower adherence [28]. Tuppin et al. [18] reported that
46 adherence to E-B treatment was decreased significantly by an age greater than 74 years,
47 confirming our findings. The prescription of complex regimens including multiple drugs
48 has been widely acknowledged as a barrier to patient adherence [29]: the longer the list
49 of drugs prescribed, the lower the adherence of patients. Chronic conditions like asthma,
50 sinoatrial bradycardia and renal disease reduce drug prescription of specific ATC
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3 groups due to adverse effects and contraindications increasing the probability of poor
4 adherence to chronic poly-therapy. A previous hospitalization with a diagnosis of
5 mental disorders decreased the odds of adherence: the mechanisms by which mental
6 disorders can affect adherence may include poor motivation, pessimism about treatment
7 effectiveness, diminished attention, memory and cognition, decreased self-care, and
8 even intentional self-harm [30]. Moreover, patients suffering from ST-elevation AMI or
9 those who had already begun E-B drugs before index AMI were more likely to be
10 adherent to chronic poly-therapy. The former have had a more severe form of the
11 disease and were probably more carefully monitored and made aware of the long-term
12 benefits generated by a continuous and persistent drug treatment. The latter were
13 already used to the chronic and continuous intake of those drugs that are recommended
14 for the secondary prevention of AMI, as a sort of “inertial effect”.

24 **Strengths and limitations of the study.**

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27 The population-based design, many patients involved and the opportunity to integrate
28 many sources of data to define and analyse the patient’s care pathway are the main
29 strengths of this study. Moreover, to our knowledge, this is the first study to evaluate
30 the adherence to E-B medications, considering the setting of AMI onset.

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33 However, the results come from a single region in Italy and may not be generalizable to
34 the other Italian regions due to possible differences in the organization of regional
35 health care services. This notwithstanding, our results are in line with results of similar
36 studies carried out in Italy [31]. Moreover, our pharmaceutical database does not
37 contain information on the prescribed daily doses and adherence to drug treatment was
38 estimated on the basis of the DDDs [32]. Using DDDs to calculate drug coverage, we
39 run the risk of not accounting for the real-life dosing of a drug when it is used for other
40 than its principal indication [33]. Therefore, misclassification of drug utilization may
41 have occurred because the dosage instructions were not known, and the defined daily
42 doses were used as the dosage assumption. However, in our study, we tried to overcome
43 this limitation by considering DDDs of betablockers reviewed by a panel of physicians,
44 seeing that in secondary prevention post AMI, DDDs are prescribed at lower dosages
45 than the main therapeutic indication.

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48 In addition, MPR method does not depend on whether patients take their medication as
49 prescribed but depends on the prescription given by physicians. Although we cannot be
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3 sure that patients actually took the drug, collecting their medications from the pharmacy
4 is a reasonable indication of an intention to continue with therapy: nevertheless, the
5 results of adherence based on claims data may be overestimated.
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9 Finally, although all available potential confounders were included in the models to
10 adjust for differences in patients' characteristics, we cannot exclude that the lack of
11 more detailed clinical data might have caused unmeasured confounding. We tried to
12 counteract this limit by applying several restrictions to obtain a cohort with patients that
13 were as homogeneous as possible.
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17 18 **Conclusions.**

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21 The availability of information systems offers the opportunity to monitor the quality of
22 care and identify weaknesses in public health-care systems. Although most attention has
23 been paid to patients with AMI admitted via the community emergency medical system
24 or through the emergency department, AMI occurring during hospitalization for other
25 medical problems is an important clinical problem.
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30 The results of our study show that, in clinical practice, pharmacotherapy for secondary
31 prevention of AMI is not fully consistent with recommended clinical guidelines,
32 especially for IH-AMI patients. Moreover, a strong association between the setting of
33 AMI onset and adherence to multiple E-B drugs was observed. Our findings provide
34 evidence on a previously unidentified groups of patients at risk for poor adherence, who
35 might benefit from greater medical attention and dedicated health-care interventions.
36 The data strongly support the need for continued efforts to improve adherence to
37 chronic poly-therapy post AMI. These findings could also stimulate efforts to
38 implement hospital strategies to give the same "attention" to IH-AMI patients as OH-
39 AMI patients. In light of the impressive and highly significant impact of the type of
40 discharge ward on the adherence to chronic poly-therapy, it is feasible that much of the
41 "disadvantage" of IH-AMI patients is attributable to the discharge processes, in
42 particular through how far they support effective transitions in and continuity of care. A
43 range of policy tools could be appropriate to reduce this gap, for example by planning
44 differentiated health care transition interventions according to the setting of AMI onset.
45 However, further studies are needed to confirm this association.
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Figure 1. Cohort selection. Exclusion criteria flow chart

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Table 1. Baseline characteristics of the study cohort

	Total cohort 25.779 (100%)	IH-AMI 1.044 (4.0%)	OH-AMI 24.735 (96.0%)
	N (%)	N (%)	N (%)
Age group (years)			
18-54	4702 (18.24)	101 (9.67)	4601 (18.6)
55-64	5886 (22.83)	149 (14.27)	5737 (23.19)
65-74	6387 (24.78)	243 (23.28)	6144 (24.84)
75-84	6122 (23.75)	360 (34.48)	5762 (23.29)
85 +	2682 (10.4)	191 (18.3)	2491 (10.07)
Age, mean(std), years	67.61 (13.20)	73.19 (12.52)	67.37 (13.18)
Gender (men)	17138 (66.48)	590 (56.51)	16548 (66.9)
ST-elevation AMI	11108 (43.09)	319 (30.56)	10789 (43.62)
Renal disease	2335 (9.06)	166 (15.9)	2169 (8.77)
Sinoatrial bradycardia	249 (0.97)	10 (0.96)	239 (0.97)
Asthma	188 (0.73)	12 (1.15)	176 (0.71)
Mental disorders	1098 (4.26)	97 (9.29)	1001 (4.05)
Ongoing concomitant treatments (distinct group of drugs) *			
0-1	7587 (29.43)	180 (17.24)	7407 (29.95)
2-4	8507 (33)	293 (28.07)	8214 (33.21)
5-7	5236 (20.31)	272 (26.05)	4964 (20.07)
8-10	2688 (10.43)	161 (15.42)	2527 (10.22)
>10	1761 (6.83)	138 (13.22)	1623 (6.56)
E-B drugs use (at least 1 prescription) *	17083 (66.27)	811 (77.68)	16272 (65.79)
Discharge ward (cardiology)	20207 (78.39)	501 (47.99)	19706 (79.67)

*, prescribed in the 6 months preceding the index admission; E-B, evidence-based

Table 2. Adherence to evidence-based medications by gender and age group

Age group (years)	β -Blockers (%)	ACEI/ARBs (%)	Antithrombotics (%)	Statins (%)
Males				
18-54	55.20	62.50	77.18	87.74
55-64	54.41	68.83	78.00	88.37
65-74	51.44	68.64	74.20	83.74
75-84	45.18	61.81	65.80	73.83
85 +	37.44	50.25	54.99	58.93
Total	51.10	64.94	73.20	82.59
Females				
18-54	48.95	49.20	66.83	76.33
55-64	51.67	61.61	68.83	78.97
65-74	52.00	65.37	65.27	76.24
75-84	48.92	61.77	58.74	67.44
85 +	40.21	53.99	51.69	51.15
Total	48.34	59.90	61.03	68.81
Whole cohort				
18-54	54.13	60.21	75.39	85.77
55-64	53.84	67.33	75.99	86.41
65-74	51.62	67.59	71.33	81.34
75-84	46.93	61.79	62.50	70.84
85 +	39.19	52.61	52.91	54.03
Total	50.18	63.25	69.12	77.97

ACEI/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Table 3. Adherence to chronic poly-therapy by gender and age group

Age group (years)	Adherence (%) (MPR \geq 75% at least 3 of 4 E-B drugs)	Adherence (%) (MPR \geq 75% for all 4 E-B drugs)
Males		
18-54	67.95	32.20
55-64	70.53	32.47
65-74	67.12	27.72
75-84	54.05	20.12
85 +	39.15	11.81
Total	64.13	27.66
Females		
18-54	51.91	23.55
55-64	60.64	25.67
65-74	58.88	24.59
75-84	51.08	18.06
85 +	36.37	11.53
Total	51.49	19.93
Whole cohort		
18-54	65.19	30.71
55-64	68.47	31.06
65-74	64.47	26.71
75-84	52.66	19.16
85 +	37.40	11.63
Total	59.89	25.07

Table 4. Variation between clusters for OH-AMI patients: the MORs

Multilevel model	Level of analysis	Explanatory variables	MOR (95% CI)	p Value
Two-level regression	(Patients) - HoD	Intercept only	1.71 (1.50 - 2.02)	<0.001
Two-level regression	(Patients) - HoD	Patient's characteristics	1.46 (1.33 - 1.64)	<0.001

HoD, hospital of discharge; MOR, median odds ratio

Table 5. Variation between clusters for IH-AMI patients: the MORs

Multilevel model	Level of analysis	Explanatory variables	MOR (95% CI)	p Value
Two-level regression	(Patients) - HoD	Intercept only	1.69 (1.43 - 2.16)	0.005
Two-level regression	(Patients) - HoD	Patient's characteristics	1.57 (1.33 - 2.06)	0.019

HoD, hospital of discharge; MOR, median odds ratio

Table 6. Association between adherence to chronic poly-therapy and symptom onset (IH-AMI VS. OH-AMI), socio-demographics and clinical characteristics.

Category	Subcategory	OR	95% CI	p Value
Symptom onset of AMI	OH-AMI	1.00	-	-
	IH-AMI	0.54	0.47 - 0.62	<0.001
Gender of patient	Male	1.00	-	-
	Female	0.75	0.71 - 0.79	<0.001
Age group (years)	(18-54)	1.00	-	-
	(55-64)	1.12	1.03 - 1.22	0.007
	(65-74)	0.98	0.90 - 1.07	0.618
	(75-84)	0.67	0.61 - 0.73	<0.001
	(85 +)	0.40	0.35 - 0.44	<0.001
Renal disease	No	1.00	-	-
	Yes	0.58	0.53 - 0.64	<0.001
Sinoatrial bradycardia	No	1.00	-	-
	Yes	0.83	0.64 - 1.08	0.171
Asthma	No	1.00	-	-
	Yes	0.51	0.37 - 0.69	<0.001
ST-elevation AMI	No	1.00	-	-
	Yes	1.48	1.40 - 1.56	<0.001
Ongoing concomitant treatments in the 6 months before index admission (number of distinct group of drugs)	(0-1)	1.00	-	-
	(2-4)	1.05	0.98 - 1.13	0.147
	(5-7)	0.92	0.84 - 1.00	0.055
	(8-10)	0.90	0.81 - 0.99	0.046
	(10 +)	0.73	0.64 - 0.82	<0.001
E-B drugs use in the 6 months before index admission (at least 1 prescription)	No	1.00	-	-
	Yes	1.57	1.47 - 1.67	<0.001
Mental disorders	No	1.00	-	-
	Yes	0.72	0.63 - 0.82	<0.001

OR, odds ratio; CI, confidence interval; E-B, evidence-based

Table 7. Adherence to evidence-based medications by the setting of AMI onset

Symptom onset of AMI	β -Blockers (%)	ACEI/ARBs (%)	Antithrombotics (%)	Statins (%)
OH-AMI	50.24	63.85	69.88	78.78
IH-AMI	48.66	48.95	51.15	58.72
Whole cohort	50.18	63.25	69.12	77.97

ACEI/ARBs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

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CONTRIBUTORSHIP STATEMENT

Salvatore Soldati contributed to the concept and design of the study, the acquisition of data from the Lazio regional health information systems, the analysis of data and the statistical methodology required for the analytic modelling, the interpretation of results, and the writing of the article.

Mirko Di Martino contributed to the design of the study, the statistical methodology required for the analytic modelling, the interpretation of results, and the writing of the article.

Davide Castagno contributed to the clinical interpretation of results, and the writing of the article.

Marina Davoli and *Daniilo Fusco* contributed to the design of the study, and the critical revision of the paper for important intellectual content, and they have given their final approval of the version submitted for publication.

All authors agree to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

COMPETING INTERESTS

The authors declare that they have non-financial associations that may be relevant to the submitted manuscript.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

DATA SHARING STATEMENT

No additional data are available.

PRIVACY LAWS

This study was carried out in full compliance with the current privacy laws. The Department of Epidemiology is legitimized by the Lazio Region Committee in

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3 managing and analyzing data from the regional health information systems for
4 epidemiological purposes.
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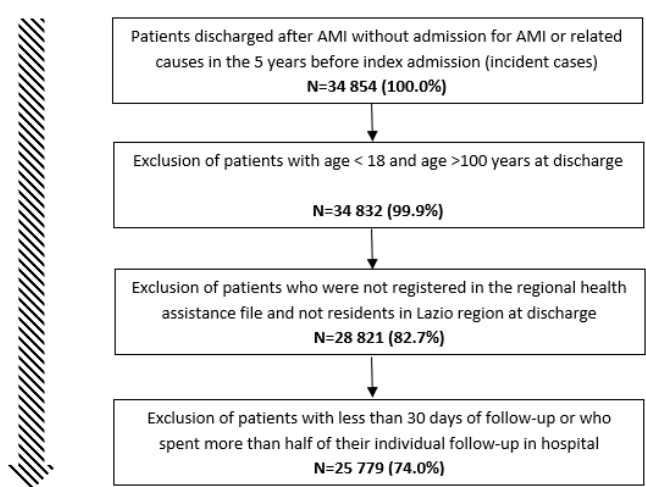


Figure 1. Cohort selection. Exclusion criteria flowchart

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any pre-specified hypotheses	4, 5
Methods			
Study design	4	Present key elements of study design early in the paper	5, 6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6, 7, 8
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5, 6, 7, 8
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	We used a multilevel approach. Matching was Not Applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, 8, 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5, 6, 7, 8, 9
Bias	9	Describe any efforts to address potential sources of bias	7, 8, 9, 13
Study size	10	Explain how the study size was arrived at	6, 7, 10, 17
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8, 9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9, 10
		(b) Describe any methods used to examine subgroups and interactions	The quantitative analysis of the

			interaction between the different levels of the healthcare system was described on pages 8 and 9.
		(c) Explain how missing data were addressed	Not Applicable. We have no missing data.
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	Not Applicable
		(e) Describe any sensitivity analyses	Not Applicable
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10, 11, 12
		(b) Give reasons for non-participation at each stage	10, 17
		(c) Consider use of a flow diagram	10, 17
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 11, 12, 18, 19, 20, 21, 22, 23
		(b) Indicate number of participants with missing data for each variable of interest	Not Applicable. We have no missing data.
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Not Applicable
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10, 11, 12, 21, 23
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Not Applicable
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11, 12, 13, 22, 23
		(b) Report category boundaries when continuous variables were categorized	11, 12, 18, 23
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	This is a multilevel study on variation in adherence to clinical guidelines. Therefore the “reporting

			method” suggested by the checklist (i.e. absolute risk measures) might probably be misleading within this framework.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11, 12, 19, 20, 22
Discussion			
Key results	18	Summarise key results with reference to study objectives	12, 13, 14, 15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15, 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13, 14, 15, 16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24 This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.