BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-042878
Article Type:	Original research
Date Submitted by the Author:	20-Jul-2020
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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

the Regional Drug Dispense Registry. The data available on each prescription includes patient's identification number, prescribing physician's number, Anatomical-Therapeutic-Chemical (ATC) code of the drug purchased, number of packs, number of units per pack, dosage, unit cost per pack and prescription date.

Any date of death was obtained from the Mortality Information System (MIS).

Data from different information systems have been integrated using a deterministic record linkage procedure based on unique and anonymous subject identifier. In this way, we created a chronological, demographical, residential, clinical, healthcare-related patient profile.

Setting and study cohort

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

Classification as to whether AMI occurred in-hospital was based on present-on-admission codes from RAD Information System. Admission code diagnosis was available in more than 98% of patients with AMI. Patients aged 18–100 years at discharge were screened for inclusion in the study.

Only incident cases of AMI were included: patients with hospital admission for AMI or related causes (i.e., percutaneous coronary intervention, bypass or surgery of the heart and great vessels) in the 5 years before index admission were excluded.

Patients who were not registered in the regional health assistance file at time of discharge from hospital were excluded (note that healthcare assistance in Italy is offered to all resident citizens without restrictions). Finally, patients who had an individual

follow-up shorter than 30 days were excluded, to give all patients the chance to achieve clinical stability and to guarantee a minimum observation period of one month for consistently estimate adherence to poly-therapy.

Patient and Public Involvement

No patient involved.

Patient characteristics

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

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

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

Follow-up

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

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

Statistical analysis

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

continuous variables (compared using Student's t-test). Considering the hierarchical data structure (patients are nested within hospitals), logistic multilevel models were performed to take into account potential intra-class correlation. The variance components were expressed in terms of Median Odds Ratio (MOR), a measure that quantifies the variability between clusters, in this case between different hospitals of discharge [20]. The MOR quantifies the variation between clusters by comparing two persons from two randomly chosen clusters. Consider two persons with the same covariates, chosen randomly from two different clusters. MOR is the median odds ratio between the person of higher propensity and the person of lower propensity [21]. This measure is always equal or greater than 1. MOR equal to 1 indicates no variability between clusters; as the variability between group increases MOR value increases. In a first step, MOR was estimated using an intercept-only model. In a second step, MOR was estimated controlling for patient characteristics, in order to ensure that of the heterogeneity of patients within groups (in terms of age, comorbidities or severity of AMI) did not influence the estimates of variance.

Logistic multilevel models were also applied to identify determinants of adherence to evidence-based drugs, taking into account the correlation within clusters. Determinants of adherence were selected based on a priori knowledge [22-23]: gender and age, discharge ward, ST-elevation AMI, use of evidence-based drugs (i.e., antithrombotics, β-blockers, ACEI/ARBs, statins) during the 6 months prior to the index admission (defined as at least one prescription), ongoing concomitant treatments (i.e., number of distinct non-evidence-based drugs) and relevant comorbidities retrieved from the hospital records for both the index admission and the two previous years.

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 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

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 significant variability in adherence to poly-therapy between different hospital was observed, even after controlling for patients' characteristics (MOR: 1.46; 95% CI: 1.34-1.64; p-value: <0.001, table 4). This variability was also observed when evaluating adherence to poly-therapy only for IH-AMI patients (MOR: 1.60; 95% CI: 1.34-2.12; p-value: 0.019).

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.

In addition, lower adherence to chronic poly-therapy was observed among patients with comorbidities. In contrast, a significantly higher adherence to poly-therapy was observed amongst patients already taking E-B drugs in the 6 months prior index admission (OR: 1.57; 95% CI: 1.47-1.67; p-value: <0.001) and amongst patients suffering from an ST-elevation MI (OR: 1.48; 95% CI: 1.40-1.56; p-value: <0.001).

After adjustment for potential confounders (including age, gender, renal disease, sinoatrial bradycardia, asthma, mental disorders, ST-elevation AMI, ongoing concomitant treatments and E-B drugs use during the 6 months prior to hospitalization)

patients suffering IH-AMI were 46% less likely to be adherent to poly-therapy as compared with OH-AMI patients (OR: 0.54; 95% CI: 0.47-0.62; p-value: <0.001).

DISCUSSION

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

Acute myocardial infarction occurring in patients who have already been admitted to the hospital for other clinical conditions is an entity that has been poorly investigated so far. In this study, amongst all the patients experiencing an AMI between January 1st 2012 and December 31th 2016 in Lazio region (see cohort selection in figure 1), the incidence of IH-AMI was 4.0%. Our study has several key findings. First, compared with OH-AMI patients, those suffering an IH-AMI were more often female, older and less likely to be discharged from cardiology wards, possibly reflecting a higher burden of comorbidities. Indeed, IH-AMI patients had more often a history of renal disease, asthma, mental disorders and more frequently were treated with beta-blockers, antithrombotic agents, ACE-Is/ARBs or statins in the 6 months prior the index event Interestingly, IH-AMI patients less frequently suffered from a ST-elevation AMI. These findings are concordant with the observations from other studies Zahn et al. [24]. Maynard et al. [3] reported that patients who had a AMI while hospitalized for other medical conditions were older, more likely to have atypical symptoms, and had higher rates of renal disease, cerebrovascular disease, congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, dementia, and cancer than patients who presented as OH-AMI to the Department of Veterans Affairs Health System.

Second, and possibly even more important, we observed that patients experiencing an IH-AMI were less likely to be adherent to E-B medications for secondary prevention of AMI during 6-month follow-up. This may be mainly explained by different patient characteristics. Another possible explanation is that, given the often complex and atypical presentations of cardiac disease in patients with other significant comorbidities. Moreover IH-AMI patients were more likely to be discharged from non-cardiological wards and this may have negatively impacted on the quality of care after the acute event.

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 ≥ 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].

We also found that female gender, older age, mental disorders, renal disease, asthma and ongoing concomitant treatments were significantly associated with non-adherence to chronic poly-therapy. Conversely, adherence was positively and significantly associated with patients who had a severe form of disease (ST-elevation AMI) and patients who have already begun E-B drugs in the 6 months before index admission.

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

drugs that are recommended for the secondary prevention of MI, as a sort of "inertial effect".

Strengths and limitations of the study.

The population-based design, a large number of patients involved and the opportunity to integrate many sources of data to define and analyse the patient's care pathway are the main strengths of this study. Moreover, to our knowledge, this is the first study to evaluate the adherence to E-B medications, taking into account the setting of AMI onset.

However, the results come from a single region in Italy and may not be generalizable to the other Italian regions due to possible differences in the organization of regional health care services. This notwithstanding, our results are in line with results of similar studies carried out in Italy [31]. Moreover, our pharmaceutical database does not contain information on the prescribed daily doses and adherence to drug treatment was estimated on the basis of the DDDs. Although this is a useful instrument for comparing the results from different studies [32], misclassification of drug utilization may have occurred.

Finally, although all available potential confounders were included in the models to adjust for differences in patients characteristics, we cannot exclude that the lack of more detailed clinical data might have caused unmeasured confounding. We tried to counteract this limit by applying a number of restrictions to obtain a cohort with patients that were as homogeneous as possible.

Conclusions.

The availability of information systems offers the opportunity to monitor the quality of care and identify weaknesses in public health-care systems. Although most attention has been paid to patients with AMI admitted via the community emergency medical system or through the emergency department, AMI occurring during hospitalization for other medical problems is an important clinical problem.

Our findings show that, in clinical practice, pharmacotherapy for secondary prevention of AMI is not fully consistent with clinical guidelines, especially for IH-AMI patients. Moreover, we found the setting of AMI onset was strongly associated with adherence to chronic poly-therapy. The results of our study may be of help to identify groups of patients at risk for non-adherence who might benefit from greater medical attention and dedicated health-care interventions.

Finally, our results suggest that efforts to improve adherence to E-B medications in clinical practice, should focus especially on patients who had an infarction during their stay in hospital, an issue that deserves further analysis.

Figure 1. Cohort selection. Exclusion criteria flow chart

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 >=75% at least 3 of 4 E-B drugs)	Adherence (%) (MPR >=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 *Danilo 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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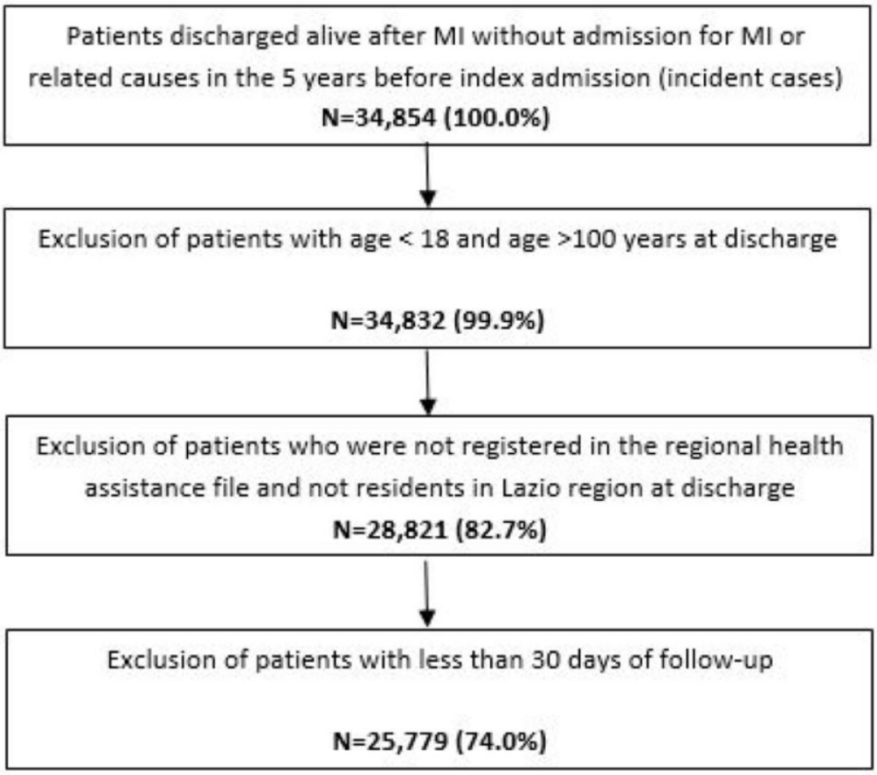

Figure1. Cohort selection. Exclusion criteria flow chart

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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5, 6, 7, 8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8, 10, 19, 20, 22
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		Cross-sectional study—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:	*BMJ Open*
Manuscript ID	bmjopen-2020-042878.R1
Article Type:	Original research
Date Submitted by the Author:	04-Nov-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>=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

acute setting to the outpatient setting. For these reasons, our research hypothesis is that the setting in which AMI develops may significantly impact on the probability of being discharge by specialized hospital wards and, consequently, on the 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 an 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 severity of patient's condition at the time of hospitalization or surgery.

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 the Regional Drug Dispense Registry. The data available on each prescription includes patient's identification number, prescribing physician's number, Anatomical-Therapeutic-Chemical (ATC) code of the drug purchased, number of packs, number of units per pack, dosage, unit cost per pack and prescription date.

Any date of death was obtained from the Mortality Information System (MIS).

Data from different information systems have been integrated using a deterministic record linkage procedure based on unique and anonymous subject identifier. In this way, we created a chronological, demographical, residential, clinical, healthcare-related patient profile.

Setting and study cohort

The present observational study was based on the population living in the Lazio region, Italy. Using data from the regional HIS, the study included a cohort of all patients discharged from hospitals between 1 January 2012 and 31 December 2016 with a diagnosis of AMI. AMI was defined according to International Classification of Diseases Ninth Revision Clinical Modification (ICD-9-CM) codes 410.xx (first or second diagnosis position). In case of multiple hospital admissions, the first admission during the study period was defined as the index admission. Subsequent hospitalizations

for any reason were recorded, and repeated admissions within 2 days of discharge were regarded as one single 'episode of care'.

Classification as to whether AMI occurred in-hospital was based on present-on-admission codes from RAD Information System. Admission code diagnosis was available in more than 98% of patients with AMI. Patients aged 18–100 years at discharge were screened for inclusion in the study.

Only incident cases of AMI were included: patients with hospital admission for AMI or related causes (i.e., percutaneous coronary intervention, bypass or surgery of the heart and great vessels) in the 5 years before index admission were excluded.

Patients who were not registered in the regional health assistance file at time of discharge from hospital were excluded (note that healthcare assistance in Italy is offered to all resident citizens without restrictions). Finally, patients who had an individual follow-up shorter than 30 days were excluded, to give all patients the chance to achieve clinical stability and to guarantee a minimum observation period of one month for consistently estimate adherence to poly-therapy.

Patient and Public Involvement

No patient involved.

Patient characteristics

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

contraindicate drug prescription of specific ATC groups due to potential adverse effects (e.g. β-blockers in patients suffering from asthma).

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

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

Follow-up

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

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 coverage provided to residents of Italy. Information about prescriptions of antithrombotics (ATC: B01AC06, B01AC04, B01AC05, B01AC22, B01AC24, B01AF01, B01AF02, B01AF03, B01AA03, B01AA07, B01AE07), β-blockers (ATC: C07), ACEI/ARBs (ATC: C09), and statins (ATC: C10AA) were retrieved for all patients. Adherence to medication was measured through the medication possession

ratio (MPR), calculated as the number of days of medication supplied during the follow-up on the basis of defined daily doses (DDDs) divided by the number of calendar days in the follow-up. Adherence to individual medications was defined as a MPR $\geq$ 0.75. Adherence to chronic poly-therapy was defined as a MPR $\geq$ 0.75 for at least three of the four evidence-based drugs [13,14].

Statistical analysis

Data are presented as frequencies and percentages for categorical variables and mean value ± standard deviation for continuous variables. Considering the hierarchical data structure (patients are nested within hospitals), logistic multilevel models were performed to take into account potential intra-class correlation. The variance components were expressed in terms of Median Odds Ratio (MOR), a measure that quantifies the variability between clusters, in this case between different hospitals of discharge. The MOR quantifies the variation between clusters by comparing two persons from two randomly chosen different clusters. Consider two persons with the same covariates, chosen randomly from two different clusters. MOR is the median odds ratio between the person of higher propensity and the person of lower propensity. This measure is always greater than or equal to 1. MOR equal to 1 indicates no variability between clusters, as the variability between group increases MOR value increases [20]. In a first step, MOR was estimated using an intercept-only model. In a second step, MOR was estimated controlling for patient characteristics, to ensure that of the heterogeneity of patients within groups (in terms of age, comorbidities, or severity of AMI) did not influence the estimates of variance.

Logistic multilevel models were also applied to identify determinants of adherence to evidence-based drugs, considering the correlation within clusters. Determinants of adherence were selected based on a priori knowledge [21-22]: gender and age, discharge ward, ST-elevation AMI, use of evidence-based drugs (i.e., antithrombotics, β-blockers, ACEI/ARBs, statins) during the 6 months prior to the index admission (defined as at least one prescription), ongoing concomitant treatments (i.e., number of distinct non-evidence-based drugs) and relevant comorbidities retrieved from the hospital records for both the index admission and the two previous years.

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

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.

In addition, lower adherence to chronic poly-therapy was observed among patients with comorbidities. In contrast, a significantly higher adherence to poly-therapy was observed amongst patients already taking E-B drugs in the 6 months prior index admission (OR: 1.57; 95% CI: 1.47-1.67; p-value: <0.001) and amongst patients suffering from an ST-elevation AMI (OR: 1.48; 95% CI: 1.40-1.56; p-value: <0.001).

Finally, a lower probability of adherence was observed in patients discharged from unspecialized hospital wards as compared with those who discharged from cardiology ward (OR: 0.58; 95% CI: 0.54-0.63; p-value: <0.001).

After adjustment for potential confounders (including age, gender, renal disease, sinoatrial bradycardia, asthma, mental disorders, ST-elevation AMI, ongoing concomitant treatments and E-B drugs use during the 6 months prior to hospitalization) patients suffering IH-AMI were 46% less likely to be adherent to poly-therapy as compared with OH-AMI patients (OR: 0.54; 95% CI: 0.47-0.62; p-value: <0.001). As summarized in table 7, IH-AMI patients showed significantly lower adherence levels for three of four E-B drugs, i.e., statins, antithrombotics and ACEI/ARBs. This "gap" was less significant for Beta-blockers.

DISCUSSION

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

Acute myocardial infarction occurring in patients who have already been admitted to the hospital for other clinical conditions is an entity that has been poorly investigated so far. In this study, amongst all the patients experiencing an AMI between January 1st 2012 and December 31th 2016 in Lazio region (see cohort selection in figure 1), the proportion of patients with IH-AMI of all patients with AMI was 4.0%. Our study has several key findings. First, compared with OH-AMI patients, those suffering an IH-AMI were more often female, older, and less likely to be discharged from cardiology wards, possibly reflecting a higher burden of comorbidities. Indeed, IH-AMI patients had more often a history of renal disease, asthma, mental disorders and more frequently were treated with beta-blockers, antithrombotic agents, ACE-Is/ARBs or statins in the 6 months prior the index event Interestingly, IH-AMI patients less frequently suffered from a ST-elevation AMI. Much of these findings are concordant with the observations from a previous study by Zahn et al. [23]. In addition, Maynard et al. [3] reported that patients who had a AMI while hospitalized for other medical conditions were older, more likely to have atypical symptoms, and had higher rates of renal disease, cerebrovascular disease, congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, dementia, and cancer than patients who presented as OH-AMI to the Department of Veterans Affairs Health System.

Second, and possibly even more important, we observed that patients experiencing an IH-AMI were less likely to be adherent to E-B medications for secondary prevention of AMI during 6-month follow-up. Moreover IH-AMI patients were more likely to be discharged from non-cardiological wards and this may have negatively impacted on the quality of care after the acute event.

Adherence to chronic poly-therapy.

Concerning the whole study period, we found that after a hospital discharge for AMI, only 60% of patients were deemed 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 ≥ 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) [24]. 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 [15] and in different countries [21,22,25].

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). Moreover, we observed a greater variability in terms of adherence to multiple recommended secondary prevention therapies for IH-AMI patients. This finding might reflect the lack of standardized and homogenous clinical care pathways within hospitals of discharge for patients who have suffered an AMI during hospitalization for other medical conditions. 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 AMI, 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, we decided not to adjust for discharge ward because we felt it could be a proxy for setting of AMI 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) [26].

We also found that female gender, older age, mental disorders, renal disease, asthma, and ongoing concomitant treatments were significantly associated with non-adherence to chronic poly-therapy. Conversely, adherence was positively and significantly associated with patients who had a severe form of disease (ST-elevation AMI) and patients who have already begun E-B drugs in the 6 months before index admission.

Our findings are consistent with the results of other investigations. It is notable that the current study demonstrates that women are receiving less optimal medical therapy in all age groups and all drug categories. The clinical relevance of gender differences varies by age and type of medication. For example, small differences are observed in the use of beta-blockers, larger differences are observed in the use of statins. Smolina et al. [27] confirmed these gender differences and showed that treatment was less often initiated in women. Older age was also found to be associated with lower adherence in several previous studies [15,17,18]. A higher prevalence of cognitive disorders, memory impairment, and limited ability to absorb new information in the elderly population have been associated with lower adherence [28]. Tuppin et al. [18] reported that adherence to E-B treatment was decreased significantly by an age greater than 74 years, confirming our findings. The prescription of complex regimens including multiple drugs has been widely acknowledged as a barrier to patient adherence [29]: the longer the list of drugs prescribed, the lower the adherence of patients. Chronic conditions like asthma, sinoatrial bradycardia and renal disease reduce drug prescription of specific ATC groups due to adverse effects and contraindications increasing the probability of poor adherence to chronic poly-therapy. A previous hospitalization with a diagnosis of mental disorders decreased the odds of adherence: the mechanisms by which mental disorders can affect adherence may include poor motivation, pessimism about treatment effectiveness, diminished attention, memory and cognition, decreased self-care, and

even intentional self-harm [30]. Moreover, patients suffering from a ST-elevation AMI or those who had already begun E-B drugs before index AMI were more likely to be adherent to chronic poly-therapy. The former have had a more severe form of the disease and were probably more carefully monitored and made aware of the long-term benefits generated by a continuous and persistent drug treatment. The latter were already used to the chronic and continuous intake of those drugs that are recommended for the secondary prevention of AMI, as a sort of "inertial effect".

Strengths and limitations of the study.

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

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

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

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

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

Conclusions.

The availability of information systems offers the opportunity to monitor the quality of care and identify weaknesses in public health-care systems. Although most attention has been paid to patients with AMI admitted via the community emergency medical system or through the emergency department, AMI occurring during hospitalization for other medical problems is an important clinical problem.

The results of our study show that, in clinical practice, pharmacotherapy for secondary prevention of AMI is not fully consistent with recommended clinical guidelines, especially for IH-AMI patients. Moreover, a strong association between the setting of AMI onset and adherence to multiple E-B drugs was observed. 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. The data strongly support the need for continued efforts to improve adherence to chronic poly-therapy post AMI. These findings could also stimulate efforts to implement hospital strategies to give the same "attention" to IH-AMI patients as OH-AMI patients. In light of the impressive and highly significant impact of the type of discharge ward on the adherence to chronic poly-therapy, it is feasible that much of the "disadvantage" of IH-AMI patients is attributable to the discharge processes, in particular through how far they support effective transitions in and continuity of care. A range of policy tools could be appropriate to reduce this gap, for example by planning differentiated health care transition interventions according to the setting of AMI onset. However, further studies are needed to confirm this association.

Figure 1. Cohort selection. Exclusion criteria flow chart

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 >=75% at least 3 of 4 E-B drugs)	Adherence (%) (MPR >=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

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 *Danilo 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

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

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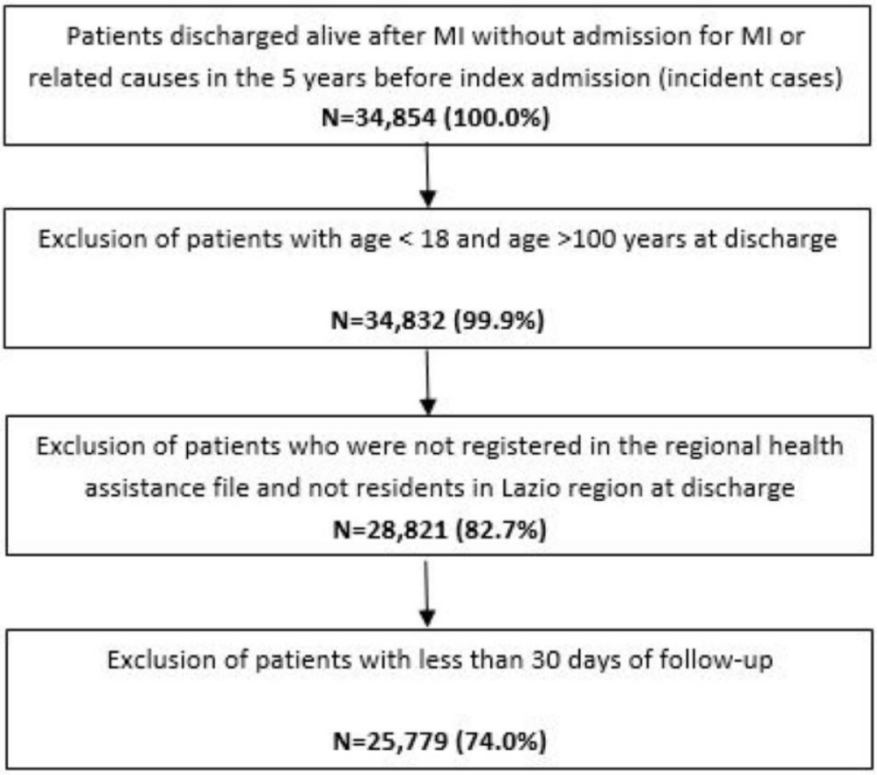

Figure1. Cohort selection. Exclusion criteria flow chart

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, 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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5, 6, 7, 8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not Applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10, 11, 12, 21, 23
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		Cross-sectional study—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:	*BMJ Open*
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>=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

acute setting to the outpatient setting. For these reasons, our research hypothesis is that the setting in which AMI develops may significantly impact on the probability of being discharge by specialized hospital wards and, consequently, on the 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).

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 severity of patient's condition at the time of hospitalization or surgery. These additional data are inserted into the RAD forms at the time of patient's hospital discharge, when the diagnostic and therapeutic care pathways are clearly defined.

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 the Regional Drug Dispense Registry. The data available on each prescription includes patient's identification number, prescribing physician's number, Anatomical-Therapeutic-Chemical (ATC) code of the drug purchased, number of packs, number of units per pack, dosage, unit cost per pack and prescription date.

Any date of death was obtained from the Mortality Information System (MIS).

Data from different information systems have been integrated using a deterministic record linkage procedure based on unique and anonymous subject identifier. In this way, we created a chronological, demographical, residential, clinical, healthcare-related patient profile.

Setting and study cohort

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

Classification as to whether AMI occurred in-hospital was based on present-on-admission codes from RAD Information System, which provides information regarding

diagnostic codes (present, absent, presence cannot be deduced from clinical documentation, not applicable) at the time of hospital presentation. AMI patients with admission code diagnosis (present) were classified as OH-AMI, patients without admission code diagnosis (absent) were classified as IH-AMI. Admission code diagnosis (present or absent) was available in more than 98% of AMI patients. To improve identification of unambiguously IH-onset AMI, we excluded patients with unclear admission code diagnosis ("presence cannot be deduced from clinical documentation" or "not applicable"). In such manner, we should be able to reduce the possible misclassification of exposure due to critical situations, in which patients may have ambiguous diagnosis at the time of hospital admission.

Patients aged 18–100 years at discharge were screened for inclusion in the study. Only incident cases of AMI were included: patients with hospital admission for AMI or related causes (i.e., percutaneous coronary intervention, bypass or surgery of the heart and great vessels) in the 5 years before index admission were excluded.

Patients who were not registered in the regional health assistance file at time of discharge from hospital were excluded (note that healthcare assistance in Italy is offered to all resident citizens without restrictions). Finally, patients who had an individual follow-up shorter than 30 days were excluded, to give all patients the chance to achieve clinical stability and to guarantee a minimum observation period of one month for consistently estimate adherence to poly-therapy.

Patient and Public Involvement

No patient involved.

Patient characteristics

Patients were characterized according to socio-demographic factors (age, gender), comorbidities that might contraindicate prescription of specific ATC group drugs, previous use of E-B drugs, previous use of other (non-E-B) medications, previous hospitalization with a diagnosis of mental disorders (ICD-9-CM codes: 290-319), hospital discharge ward and ST-elevation myocardial infarction (STEMI) as indicator of severity of disease. STEMI patients were identified using ICD-9-CM diagnosis codes 410.xx, excluding 410.7x (non-ST-elevation AMI) and 410.9x (acute AMI, not otherwise specified) in any diagnostic position. The following diseases were assessed

by health ticket exemption or during hospitalization or emergency department visit for index admission as well as in the 2 years preceding the beginning of follow-up: asthma (ICD-9-CM diagnosis code 493), renal disease (ICD-9-CM diagnosis codes: 582-588, V42.0, V45.1, V56, ICD-9-CM procedure codes: 38.95, 39.95, 54.98, 55.6), sinoatrial bradycardia (ICD-9-CM diagnosis code 427.8). These clinical conditions might contraindicate drug prescription of specific ATC groups due to potential adverse effects (e.g., β-blockers in patients suffering from asthma).

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

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

Follow-up

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

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

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

Statistical analysis

Data are presented as frequencies and percentages for categorical variables and mean value ± standard deviation for continuous variables. Considering the hierarchical data structure (patients are nested within hospitals), logistic multilevel models were performed to take into account potential intra-class correlation. The variance components were expressed in terms of Median Odds Ratio (MOR), a measure that quantifies the variability between clusters, in this case between different hospitals of discharge. The MOR quantifies the variation between clusters by comparing two persons from two randomly chosen different clusters. Consider two persons with the same covariates, chosen randomly from two different clusters. MOR is the median odds ratio between the person of higher propensity and the person of lower propensity. This measure is always greater than or equal to 1. MOR equal to 1 indicates no variability between clusters, as the variability between group increases MOR value increases [20]. In a first step, MOR was estimated using an intercept-only model. In a second step, MOR was estimated controlling for patient characteristics, to ensure that of the heterogeneity of patients within groups (in terms of age, comorbidities, or severity of AMI) did not influence the estimates of variance.

Logistic multilevel models were also applied to identify determinants of adherence to evidence-based drugs, considering the correlation within clusters. Determinants of adherence were selected based on a priori knowledge [21-22]: gender and age, discharge ward, ST-elevation AMI, use of evidence-based drugs (i.e., antithrombotics,

β-blockers, ACEI/ARBs, statins) during the 6 months prior to the index admission (defined as at least one prescription), ongoing concomitant treatments (i.e., number of distinct non-evidence-based drugs) and relevant comorbidities retrieved from the hospital records for both the index admission and the two previous years.

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 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.

In addition, lower adherence to chronic poly-therapy was observed among patients with comorbidities. In contrast, a significantly higher adherence to poly-therapy was observed amongst patients already taking E-B drugs in the 6 months prior index admission (OR: 1.57; 95% CI: 1.47-1.67; p-value: <0.001) and amongst patients suffering from an ST-elevation AMI (OR: 1.48; 95% CI: 1.40-1.56; p-value: <0.001). Finally, a lower probability of adherence was observed in patients discharged from unspecialized hospital wards as compared with those who discharged from cardiology ward (OR: 0.58; 95% CI: 0.54-0.63; p-value: <0.001).

After adjustment for potential confounders (including age, gender, renal disease, sinoatrial bradycardia, asthma, mental disorders, ST-elevation AMI, ongoing concomitant treatments, and E-B drugs use during the 6 months prior to hospitalization) patients suffering IH-AMI were 46% less likely to be adherent to poly-therapy as compared with OH-AMI patients (OR: 0.54; 95% CI: 0.47-0.62; p-value: <0.001). As summarized in table 7, IH-AMI patients showed significantly lower adherence levels for three of four E-B drugs, i.e., statins, antithrombotics and ACEI/ARBs. This "gap" was less significant for Beta-blockers.

DISCUSSION

Prevalence and clinical characteristics of IH-AMI patients.

Acute myocardial infarction occurring in patients who have already been admitted to the hospital for other clinical conditions is an entity that has been poorly investigated so far. In this study, amongst all the patients experiencing AMI between January 1st 2012 and December 31th 2016 in Lazio region (see cohort selection in figure 1), the proportion of patients with IH-AMI of all patients with AMI was 4.0%. Our study has several key findings. First, compared with OH-AMI patients, those suffering IH-AMI were more often female, older, and less likely to be discharged from cardiology wards, possibly reflecting a higher burden of comorbidities. Indeed, IH-AMI patients had more often a history of renal disease, asthma, mental disorders and more frequently were treated with beta-blockers, antithrombotic agents, ACE-Is/ARBs or statins in the 6 months prior the index event Interestingly, IH-AMI patients less frequently suffered from ST-elevation AMI. Much of these findings are concordant with the observations from a previous study by Zahn et al. [23]. In addition, Maynard et al. [3] reported that patients who had

AMI while hospitalized for other medical conditions were older, more likely to have atypical symptoms, and had higher rates of renal disease, cerebrovascular disease, congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, dementia, and cancer than patients who presented as OH-AMI to the Department of Veterans Affairs Health System.

Second, and possibly even more important, we observed that patients experiencing IH-AMI were less likely to be adherent to E-B medications for secondary prevention of AMI during 6-month follow-up. Moreover IH-AMI patients were more likely to be discharged from non-cardiological wards and this may have negatively impacted on the quality of care after the acute event.

Adherence to chronic poly-therapy.

Concerning the whole study period, we found that after a hospital discharge for AMI, only 60% of patients were deemed adherent to poly-therapy in the following 6 months. Treatments with proven benefit in secondary prevention following 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) [24]. 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 [15] and in different countries [21,22,25].

To the best of our knowledge our study was the first to assess, whether adherence differed between patients who had IH-AMI as compared with those who experienced OH-AMI. Interestingly, the setting of AMI onset had a significant impact on poly-therapy adherence. In fact, patients who had AMI during their hospital stay were less likely to be adherent to chronic poly-therapy compared with patients who had 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). Moreover, we observed a greater variability in terms of adherence to multiple recommended secondary prevention therapies for IH-AMI patients. This

finding might reflect the lack of standardized and homogenous clinical care pathways within hospitals of discharge for patients who have suffered AMI during hospitalization for other medical conditions. 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 AMI, 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, we decided not to adjust for discharge ward because we felt it could be a proxy for setting of AMI 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 OH-AMI. In this situation, an adjustment for discharge ward, could have introduced (rather than eliminated) a bias (overadjustment) [26].

We also found that female gender, older age, mental disorders, renal disease, asthma, and ongoing concomitant treatments were significantly associated with non-adherence to chronic poly-therapy. Conversely, adherence was positively and significantly associated with patients who had a severe form of disease (ST-elevation AMI) and patients who have already begun E-B drugs in the 6 months before index admission.

Our findings are consistent with the results of other investigations. It is notable that the current study demonstrates that women are receiving less optimal medical therapy in all age groups and all drug categories. The clinical relevance of gender differences varies by age and type of medication. For example, small differences are observed in the use of beta-blockers, larger differences are observed in the use of statins. Smolina et al. [27] confirmed these gender differences and showed that treatment was less often initiated in women. Older age was also found to be associated with lower adherence in several previous studies [15,17,18]. A higher prevalence of cognitive disorders, memory impairment, and limited ability to absorb new information in the elderly population have been associated with lower adherence [28]. Tuppin et al. [18] reported that adherence to E-B treatment was decreased significantly by an age greater than 74 years, confirming our findings. The prescription of complex regimens including multiple drugs has been widely acknowledged as a barrier to patient adherence [29]: the longer the list of drugs prescribed, the lower the adherence of patients. Chronic conditions like asthma, sinoatrial bradycardia and renal disease reduce drug prescription of specific ATC

groups due to adverse effects and contraindications increasing the probability of poor adherence to chronic poly-therapy. A previous hospitalization with a diagnosis of mental disorders decreased the odds of adherence: the mechanisms by which mental disorders can affect adherence may include poor motivation, pessimism about treatment effectiveness, diminished attention, memory and cognition, decreased self-care, and even intentional self-harm [30]. Moreover, patients suffering from ST-elevation AMI or those who had already begun E-B drugs before index AMI were more likely to be adherent to chronic poly-therapy. The former have had a more severe form of the disease and were probably more carefully monitored and made aware of the long-term benefits generated by a continuous and persistent drug treatment. The latter were already used to the chronic and continuous intake of those drugs that are recommended for the secondary prevention of AMI, as a sort of "inertial effect".

Strengths and limitations of the study.

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

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

In addition, MPR method does not depend on whether patients take their medication as prescribed but depends on the prescription given by physicians. Although we cannot be

sure that patients actually took the drug, collecting their medications from the pharmacy is a reasonable indication of an intention to continue with therapy: nevertheless, the results of adherence based on claims data may be overestimated.

Finally, although all available potential confounders were included in the models to adjust for differences in patients' characteristics, we cannot exclude that the lack of more detailed clinical data might have caused unmeasured confounding. We tried to counteract this limit by applying several restrictions to obtain a cohort with patients that were as homogeneous as possible.

Conclusions.

The availability of information systems offers the opportunity to monitor the quality of care and identify weaknesses in public health-care systems. Although most attention has been paid to patients with AMI admitted via the community emergency medical system or through the emergency department, AMI occurring during hospitalization for other medical problems is an important clinical problem.

The results of our study show that, in clinical practice, pharmacotherapy for secondary prevention of AMI is not fully consistent with recommended clinical guidelines, especially for IH-AMI patients. Moreover, a strong association between the setting of AMI onset and adherence to multiple E-B drugs was observed. 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. The data strongly support the need for continued efforts to improve adherence to chronic poly-therapy post AMI. These findings could also stimulate efforts to implement hospital strategies to give the same "attention" to IH-AMI patients as OH-AMI patients. In light of the impressive and highly significant impact of the type of discharge ward on the adherence to chronic poly-therapy, it is feasible that much of the "disadvantage" of IH-AMI patients is attributable to the discharge processes, in particular through how far they support effective transitions in and continuity of care. A range of policy tools could be appropriate to reduce this gap, for example by planning differentiated health care transition interventions according to the setting of AMI onset. However, further studies are needed to confirm this association.

Figure 1. Cohort selection. Exclusion criteria flow chart

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 >=75% at least 3 of 4 E-B drugs)	Adherence (%) (MPR >=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

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 *Danilo 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

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

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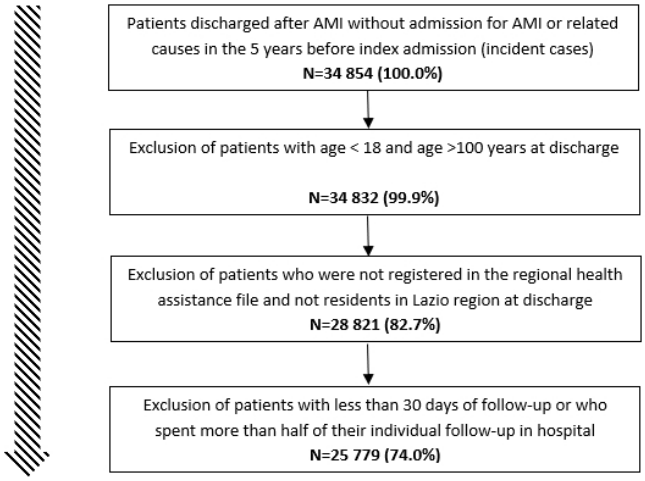

Figure 1. Cohort selection. Exclusion criteria flowchart

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*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—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 *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5, 6, 7, 8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—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*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—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) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Not Applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10, 11, 12, 21, 23
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		Cross-sectional study—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.