PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	In-hospital myocardial infarction and adherence to evidence-based drug therapies: a real-world evaluation
AUTHORS	Soldati, Salvatore; Di Martino, Mirko; Castagno, Davide; Davoli, Marina; Fusco, Danilo

VERSION 1 – REVIEW

REVIEWER	Jacopo Lenzi University of Bologna, Italy
REVIEW RETURNED	26-Aug-2020

GENERAL COMMENTS	The study by Salvatore Soldati and colleagues aimed to investigate the adherence to secondary prevention poly-therapy in patients who experienced an AMI before entering the hospital versus those who experienced an AMI during hospital stay. The paper is interesting and well written, but some issues should be cleared up by the authors. Here are my comments: 1) Introduction, fourth paragraph (Moreover […] them). This part is a little confusing. First, you say that there is a substantial variability in medication adherence across hospitals; then you say that the setting in which an AMI develops may have a strong impact on medication adherence. Put in this way, it seems that the “settings” are different types of hospitals (e.g., teaching versus non-teaching) or wards (e.g., cardiology versus internal medicine). I suggest that you better connect these two parts and elaborate more on your hypothesis. A grammatical mistake is also present on the first line (“exist(s)”). 2) Data sources, third paragraph. What about the accuracy of present-on-admission (POA) coding in the administrative hospital system of Lazio? This has been quite of an issue in the United States and other countries. Please also take a look at the second to last line (“[…] and also (it be able) to […]”). 3) Patient characteristics, fourth line. Did you consider gathering information about mental disorders from additional data sources? In Emilia-Romagna we have the SISM (Sistema informativo salute mentale) and the SDRES (Scheda di dimissione residenziale). 4) Setting and study cohort, first two lines. A comma is missing between “region” and “Italy”. 5) Statistical analysis, first lines. “Column-wise frequencies” sounds odd. I would just say “frequencies”.

	6) Statistical analysis, first lines. Pearson's chi-squared test and Student's t-test are mentioned, but differences in the case mix of OH- and IH-AMI patients were evaluated informally (or so it seems). This is not a bad idea since you have tons of records, but I would remove any reference to the chi-squared test and t-test. 7) Discussion, second paragraph. The sentence "This may be mainly explained by different patient characteristics" is a little surprising, since you did your best to adjust for patient characteristics. Are you referring to relevant clinical variables, such as AMI severity or BMI, that are not present in the administrative databases? Please elaborate more on that. 8) Discussion, second paragraph. The sentence "Another possible […] comorbidities" seems truncated. 9) Discussion, fourth paragraph. You cite some references (16–18) that support the specialist management of AMI. Why did you not verify this on your own data? See the point below for further considerations. 10) Discussion, fourth paragraph. I am not one hundred percent sure that including the type of ward in the model would lead to an over-adjustment bias. This variable is a proxy for the setting of AMI onset, but is also a proxy for many potential aspects of care that have an impact on medication adherence. These are, for instance, cardiology follow-up visits and enrollment in post-AMI care pathways. By showing that the lower adherence of IH-AMI patients is largely or partly explained by the ward of discharge, you would be able to discuss aspects of care that are very important to patients and stakeholders. However, if you really think that the type of ward should not be included in the model, I invite you to provide more convincing arguments (is it an intermediate variable or descending proxy? why does this not apply to the other variables?). In this case, you should also remove "discharge ward" from the second paragraph of the Statistical analysis section. 11) General comment. A part of the paper is dedicated to quantifying between-hospital variability using the MOR, but this result is never discussed hereinafter. 12) General comment. I suggest that you include the discharge year in your regression model. Post-acute/chronic care and POA coding practices might have evolved between 2012 and 2016.

REVIEWER	Bertil Lindahl Department of medical sciences, Uppsala Universitet, Sweden
REVIEW RETURNED	29-Aug-2020

GENERAL COMMENTS	The main objectives of this study were to measure the adherence to chronic poly-therapy following an AMI; and to identify determinants of adherence to E-B drugs specifically focusing on the potential association between AMI with onset outside hospital and in hospital, respectively (i.e. IH-AMI vs. OHAMI). The authors conclude that pharmacotherapy after AMI is not consistent with clinical guidelines, especially for IH-AMI patients, and that it is possible to identify groups of patients at risk for poor adherence who might benefit from greater medical attention and dedicated health-care interventions. The novelty of the study is the focus on

	patients with in-hospital onset of AMI. I have several questions and comments. General: 1. The article would benefit from a language review. Methods: 2. The diagnosis code on admission from the RAD register is critical for the definition of IH-AMI and OH-AMI, respectively. Please, explain a little more in detail how the admission diagnosis is made. Many patients at the time of admission to the CCU/ward don't have a definite diagnosis, but is submitted as "suspected AMI", other may be admitted as "unstable angina" which after further testing turned out to meet the criteria for diagnosis of AMI. Can we be sure that the patients classified as IH-AMI really had the onset of the AMI in-hospital? 3. The authors wanted to only include incident cases of AMI. Therefore, patients hospitalized for AMI the previous 5 year were excluded. This seems reasonable, but why was patients with a PCI or CABG performed the previous 5 years expected regardless of the underlying diagnosis? 4. For the definition of adherence to medication the drug dispense registry was used and the MPR was calculated. The drug adherence measured by MPR is dependent on 1) that the drug is prescribed by a physician and 2) that the patient goes to a pharmacy and picks up the prescribed medicine. Do you have any information on to what extent the E-B drugs actually were prescribed at the time of discharge? For how long consumption can a drug be prescribed in Italy? If a drug can be prescribed for 6 months (e.g 180 tablets of betablocker, 1 tabl o.d., will last for the whole 6 month period and per definition give a MPR of 1, even if the patient may have stopped taking the medication after a few weeks). In the discussion section this should be discussed. Is it the adherence to guideline medication by the health care, by the patient, or by a combination that is studied? Results 5. The study was performed over a 5-year period. Was there any time trend in the adherence to E-B drugs during the period? Discussion 6. Please discuss the importance of the "health-care factor" and the "patient factor" for the adherence to the drugs, see point 4 above. MPR will give a over-estimating of the true adherence to the drugs, since we don't know if the patients actually take the drugs. 7. Please also discuss the potential effects of using DDD instead of the individual drug dosage for the comparison of MPR between the different drug classes. In the study by Grimmsmann T and Himmel W (Discrepancies between prescribed and defined daily doses: a matter of patients or drug classes? Eur J Clin Pharmacol. 2011 Aug; 67(8): 847–854.) it was shown that for the "true" betablocker" dosage was significantly lower than the DDD and in contrast significantly higher for ACE-inhibitors. 8. I disagree with the final statement (page 16): "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." Since, patients with OH-AMI constitute 96% of the AMIs and also has poor drug adherence, although not as poor as IH-AMI, it would be important to focus on improving the adherence regardless of where the AMI starts. However, I agree that patients with IH-AMI deserve further attention.

REVIEWER	Maarit Korhonen University of Turku Finland
REVIEW RETURNED	08-Sep-2020

GENERAL COMMENTS	Thank you for providing me the opportunity to review this paper. While it provides information on a novel predictor of adherence to secondary prevention medications of acute myocardial infarction, the clinical importance of this predictor remains unclear. In addition, I found that the manuscript includes some text which could be considered as plagiarism and overall the use of references is sloppy. This study aimed to assess adherence to multiple guideline recommended secondary prevention medications after hospitalization for/including acute myocardial infarction (AMI) and to determine the associations of adherence and the setting of AMI onset (in- vs out of hospital) as well as a few other predictors. The study population consisted of >25 000 hospitalized patients with AMI from one region of Italy in 2012-16. The data came from comprehensive health registers covering the whole population of the region. The evidence-based medications considered were antithrombotics, betablockers, ACE inhibitors/angiotensin receptor blockers (ARB), and statins. Adherence was measured based on prescription claims during a 6-month period after the discharge, using medication possession ratio (MPR). Adherence (MPR >=75% during the 6-month follow-up) to at least 3 medications ("polytherapy") was the main outcome. In addition to the setting of AMI onset, the following predictors for adherence were considered: age, gender, type of AMI (ST vs non-ST elevation), number of other medications in use prior to hospitalization, and relevant contraindications to at least one of the 4 evidence-based medication categories. In summary, 60% of the patients were deemed adherent to polytherapy. A strong association between the AMI setting and adherence was observed, those with in-hospital AMI being about twice as likely to be non-adherent to polytherapy. The manuscript provides evidence on a previously unidentified predictor of non-adherence to evidence-based medication post-AMI. Another strength is that the authors considered between hospital variation in their data analyses which is often overlooked in similar studies. However, the clinical consequences of the findings remain somewhat unclear. In addition, I have concerns related to scientific writing. My detailed comments are as follows: INTRODUCTION 1) The first paragraph of the introduction is to a large extent plagiarized from Bradley et al. Incidence, Risk Factors, and Outcomes Associated With In-Hospital Acute Myocardial Infarction. JAMA Netw Open 2019 Jan; 2(1): e187348 which reads as follows: "Most studies of acute myocardial infarction (AMI) epidemiology and treatment have focused on patients who experience the onset of AMI outside of the hospital. Insights from these studies have informed risk factors and optimal treatment of AMI, which have led to subsequent reductions in AMI incidence and mortality.[1,2] It is increasingly recognized that AMI also occurs among patients already hospitalized for other conditions.[3,4] …"

	References 1-4 are the same in both papers while the current manuscript does not acknowledge Bradley et al (2019) even as a reference. In the first sentence, the authors of the current manuscript have done some rewording by replacing the expression "patients who experience the onset of AMI outside of the hospital" by "outpatients". However, this seems misleading as the individuals hospitalized for their first AMI are not outpatients (if an outpatient is defined as a patient who receives medical treatment without being admitted to a hospital) Furthermore, the authors state "little is known about the incidence, clinical characteristics and management of patients experiencing in-hospital AMI (IN-AMI)". However, Bradley et al report on these in their paper. In contrast, the current manuscript does not deal with incidence of IN-AMI (see the comment #2) and provides very limited information on IN-AMI patients' clinical characteristics or management other than usage patterns of the 4 guideline-recommended drug groups during the 6 months post-discharge. 2) The word "incidence" is used incorrectly. Incidence of IN-AMI would be calculated as the number of patients with IN-AMI over all individuals hospitalized during the observation period (similarly to Bradley et al.) or as the number of IN-AMI per population with potential exclusions of individuals with prior hospitalizations for related causes from the denominator. Accordingly, in the 2nd pg of the INTRODUCTION, the word "incidence" should be replaced by "onset of AMI". In the DISCUSSION, p. 13, line 23, "incidence" should be replaced e.g. by the following expression "proportion of patients with IN-AMI of all patients with AMI surviving 30 days without rehospitalization after hospital discharge". It would be important to cite the Italian guidelines on secondary prevention after AMI and point out that/if they were similar to the international guidelines cited (during the observation period). For example, since 2015 the European Cardiology Society (ECS) guidelines have recommended use of betablockers in post-AMI patients with heart failure and without contraindications only. In any case, it would be important to discuss the differences between the current and prior guidelines in some point of the manuscript. In particular, the role of betablockers in the treatment of post AMI patients has been questioned (e.g. Korhonen MJ, Robinson JG, Annis IE, Hickson RP, Bell JS, Hartikainen J, Fang G. Adherence Tradeoff to Multiple Preventive Therapies and All-Cause Mortality After Acute Myocardial Infarction. J Am Coll Cardiol. 2017. 70:1543-54) 3) References #7-11 mentioned in the 1st sentence of 4th pg do not include information on the association between

	long-term adherence and survival. E.g. ref #7 does not report anything on long-term adherence to drug therapy nor its benefits after the discharge, the aim being to study "the impact of evidence based medical treatments and coronary revascularisation during or near the event". These authors state "we have no record of ongoing cardioprotective treatment beyond that given at discharge". Ref #9: "We examined the discharge use of medications among 5833 hospital survivors who did not have any contraindications to antiplatelet/anticoagulant, β-blocker, angiotensin-converting enzyme inhibitor, or lipid-modifying therapies." That is, survival benefits of discharge use of these medications were assessed, not those of long-term adherence. References reporting on the association between long-term adherence (6+months) and survival include e.g. ref #13 and the following: Choudhry NK, Glynn RJ, Avorn J, et al. Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. Am Heart J. 2014;167:51–8. e5 Hamood H, Hamood R, Green MS, Almog R. Effect of adherence to evidence-based therapy after acute myocardial infarction on all-cause mortality. Pharmacoepidemiology Drug Saf. 2015;24:1093–104. Korhonen MJ, Robinson JG, Annis IE, Hickson RP, Bell JS, Hartikainen J, Fang G. Adherence Tradeoff to Multiple Preventive Therapies and All-Cause Mortality After Acute Myocardial Infarction. J Am Coll Cardiol. 2017. 70:1543-54 4) Please add references to the 1st sentence of 5th pg to support your statement that substantial variation in AMI treatment exists between hospitals. In addition, the information in the 5th paragraph could be preferably presented after the main objectives. 5) Overall, the introduction is not convincing in making the case for studying the setting of AMI onset as a potential predictor for adherence. What overall is known about predictors of adherence to secondary prevention medications post-AMI and why do the authors think the setting would be of importance (e.g. prior knowledge about the effect of discharge department could be briefly described here)? METHODS Data sources 6) The last sentence of the 3rd pg (p. 6, lines 45-49) is unclear: Should patient's severity be severity of patient's condition? Are some words missing from the last part of the sentence "it be able to support …". Please clarify or delete. 7) P. 7, line 9: What is the dosage mentioned here? Do you mean strength of a tablet or other unit? It would be important to state here that no information on dosage instructions are available in the data source. 8) Is there any information on discharge destination (home vs nursing home/assisted care facility)? This information would be important as individuals discharged to nursing

homes are likely to be frailer and have lower life-expectancy than those discharged to their homes. In nursing homes or residential care settings individuals are not necessarily responsible for administering their medications and these facilities may even have hospital admission avoidance or deprescribing programs in place. If patients with IH-AMI were more likely to be discharged to nursing homes or similar settings, they may represent a different subset with different goals of care compared to the rest of the post-AMI patients.

Setting and study cohort

9) What was the rationale for restricting the study cohort to incident cases of AMI?

Patient characteristics

10) What is health ticket exemption mentioned on p. 8, lines 30-31? Was there any information on outpatient diagnoses of e.g. asthma? Presence of asthma is likely to be misclassified (underestimated) when relying on hospitalizations or emergency room visits as the information source.

Definition of exposure and outcome

11) It seems that the outcome is a mixture of prescriber's adherence to guidelines and patient's refill adherence.
12) How common is in this health system that patients fill their prescriptions already at the hospital pharmacy on their way home? How long is a prescription valid (or was during the observation period)? Do reimbursement rules restrict the days' supply dispensed per each transaction. In many countries, only a 1- month supply is reimbursed while e.g. in Finland a maximum of 3 months' supply can be reimbursed per transaction. If patients had filled prescriptions for extended periods of time prior to index hospitalization, they may have had E-B medications on hand when discharged from hospital. Ignoring those unused tablets available to the patient at discharge may have led to underestimation of adherence. Could authors comment on this?
13) Add reference to the WHO ATC/DDD classification system and specify which year's version was used.
14) Were there any combination products of statins (C10B) available in Italy during the study years?

Statistical analyses

15) While multilevel modeling is a clear strength of this study, use of logistic regression model for measuring the association between the exposure(s) and outcome is not optimal. The period over which adherence was measured varies from 30 days up to 180 days. Those patients with IN-AMI have high mortality (up to 60% at 1 year according to Bradley et al. 2019). Their shorter follow-up may reflect lower life-expectancy and different goals of care – which may be a more important reason for lower adherence than the setting of AMI.

RESULTS

16) The authors seem to have information on length of the index hospital stay. Its mean/median should be reported for those with IN and OH-AMI.

17) For the reasons listed in comment #15, the mean/median follow-up times should be presented for all patients and those with IN and OH-AMI separately.
18) It would be important to report how many patients filled at least 1 prescription for each drug category. Some previous studies on adherence have restricted their study populations to those with at least one fill of each E-B medication (initiators) within a month post-discharge (e.g. Korhonen et al. 2017). In addition, these rates would more closely reflect prescriber's adherence to guidelines than the 6-month adherence.

19) Adherence to each drug category by the setting of AMI onset should be added to Table 2.
20) If it is possible that in the Italian system patients may have had large quantities of unused tablets on hand at the time of hospital discharge, a sensitivity analysis which takes these into account should be conducted.

DISCUSSION

21) On p. 12, line 37, the authors state that their findings in terms of differences in characteristics between IN and OH-AMI patients accord with those by Zahn et al. However, this is only partly true as in the study by Zahn et al (ref #30) patients with IN-AMI were LESS likely to have chronic obstructive lung disease and less likely to have used aspirin, betablockers and ACE inhibitors than those with OH-AMI.
22) In the 2nd pg, lines 48-60, the authors discuss the lower prevalence of adherence among patients with IN-AMI and reasons for this. Discussion on potential differences in life-expectancy (reflected e.g. by the follow-up times. In case other diagnoses associated with the hospital stay were available, they could clarify this issue too) and goals of care should be added. Could IN-AMI just be a proxy for frailty?
23) Lines 53-54: "Another possible explanation is that, given the often complex and atypical presentations of cardiac disease in patients with other significant comorbidities." – incomplete sentence?
24) Under the heading Adherence to chronic poly-therapy, the authors seem to focus on underprescribing of evidence-based therapies, yet their outcome is adherence measured by MPR over a 6-month period. This measure is likely to mix prescriber's decisions with patient's/carer's decisions.
25) The authors discuss gender differences in adherence and state that women are still considered at lower risk of AMI - this is counterintuitive as all patients in this study had an AMI.
26) Overall, specific references should be added to the sentences stating what has been found in prior studies, e.g. to the statement that cognitive disorders etc. have been associated with lower adherence.
27) Is the expression "inertial effect" authors' own - if not a reference is needed. It is not quite clear what authors mean by this effect here.

Strengths and limitations

	28) Defined daily dose (DDD) is not a necessarily useful tool for estimating the prescribed daily dose of an individual drug when measuring adherence. As the prescribed daily doses are likely to vary across populations, the results from different studies are likely to be biased but not to the same extent; therefore, comparison of the results on adherence measured using DDD from different studies is not easy either. I suggest that the author delete the first part of the sentence "Although this is a useful instrument for comparing the results from different studies" and just state that misclassification of adherence may have occurred because the dosage instructions were not known and the defined daily doses were used as the dosage assumption. 29) Another limitation to the study is that it is not known whether it was the physician's or patient's/carer's decision not to adhere to the guideline-recommended drug therapy. This is an important limitation as it is difficult to say who should be the target of the potential adherence intervention based on the results of this study. ABSTRACT should be revised to reflect the changes (e.g. wording) in other parts of the manuscript. Minor issues Reference #15 is followed by #19 in the text, #16-18 are mentioned after #24.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1. Comments to the Author

Jacopo Lenzi (Reviewer 1): The study by Salvatore Soldati and colleagues aimed to investigate the adherence to secondary prevention poly-therapy in patients who experienced an AMI before entering the hospital versus those who experienced an AMI during hospital stay. The paper is interesting and well written, but some issues should be cleared up by the authors. Here are my comments:

1) Introduction, fourth paragraph (Moreover […] them). This part is a little confusing. First, you say that there is a substantial variability in medication adherence across hospitals; then you say that the setting in which an AMI develops may have a strong impact on medication adherence. Put in this way, it seems that the "settings" are different types of hospitals (e.g., teaching versus non-teaching) or wards (e.g., cardiology versus internal medicine). I suggest that you better connect these two parts and elaborate more on your hypothesis. A grammatical mistake is also present on the first line ("exist(s)").

The fourth paragraph of the "Introduction" section was deleted because, after reading the reviewer's suggestion, the authors felt it was too vague and ambiguous. In addition, we revised the whole "Introduction" section in a more explicative manner.

2) Data sources, third paragraph. What about the accuracy of present-on-admission (POA) coding in the administrative hospital system of Lazio? This has been quite of an issue in the United States and other countries. Please also take a look at the second to last line ("[…] and also (it be able) to […]").

This is an interesting topic, also raised by the referee #2. Quality of data and accuracy of diagnostic codes are crucial. 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, not applicable, presence cannot be deduced from clinical documentation) 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 ("not applicable" or "presence cannot be deduced from clinical documentation"). In such manner, we should be able to reduce a possible misclassification of exposure due to critical situations, in which patients did not have a definite diagnosis ("suspected AMI") at the time of hospital admission. Moreover, in the Lazio Region, is currently active the Regional Program for Evaluation of Outcomes of Health Care Interventions (P.Re.Val.E.). In Italy, since 2006, this program performs comparative analyses of hospital care, and more than 70 outcome indicators of inpatient care are evaluated [Fusco D, et al. P.Re.Val.E.: outcome research program for the evaluation of health care quality in Lazio, Italy. BMC Health Serv Res. 2012 Jan 27; 12:25]. The results provided by the P.Re.Val.E. are updated every year and are publicly available. This Program performs continuous audit procedures on the accuracy of ICD diagnostic codes, through a "constant" dialogue between the Department of Epidemiology of the Lazio Region and Lazio hospitals. For all of these reasons, the authors can ensure the reviewer that IH-AMI patients really had an infarction during their hospital stay.
Regarding to the text at the second to last line ("[…] and also (it be able) to […]") in the "Data sources" paragraph of the "Methods" section, now was deleted because it was misleading.

3) Patient characteristics, fourth line. Did you consider gathering information about mental disorders from additional data sources? In Emilia-Romagna we have the SISM (Sistema informativo salute mentale) and the SDRES (Scheda di dimissione residenziale).

The availability of additional information systems about mental disorders would certainly be very useful. Unfortunately, these additional data sources have not been integrated with Health Information Systems of the Lazio Region. Therefore, to identify previous hospitalization with a diagnosis of mental disorders we used the following ICD-9-CM codes: 290-319, using data from regional hospital information systems (HIS) and regional healthcare emergency information (HEIS).

4) Setting and study cohort, first two lines. A comma is missing between "region" and "Italy".

We apologize for the mistake. We added a comma between "region" and "Italy" in the "Setting and study cohort" paragraph of the "Methods" section.

5) Statistical analysis, first lines. “Column-wise frequencies” sounds odd. I would just say “frequencies”.

We agree with the referee and we replaced “column-wise frequencies” by “frequencies” in the “Statistical analysis” paragraph of the “Methods” section.

6) Statistical analysis, first lines. Pearson’s chi-squared test and Student’s t-test are mentioned, but differences in the case mix of OH- and IH-AMI patients were evaluated informally (or so it seems). This is not a bad idea since you have tons of records, but I would remove any reference to the chi-squared test and t-test.

We removed any reference to the chi-squared test and t-test in the “Statistical analysis” paragraph of the “Methods” section, as suggested by the reviewer.

7) Discussion, second paragraph. The sentence “This may be mainly explained by different patient characteristics” is a little surprising, since you did your best to adjust for patient characteristics. Are you referring to relevant clinical variables, such as AMI severity or BMI, that are not present in the administrative databases? Please elaborate more on that. 8) Discussion, second paragraph. The sentence “Another possible […] comorbidities” seems truncated.

The reviewer is right. We were referring to unmeasured confounding due to clinical variables which are not available in our regional health information systems. After a critical revision of the whole “Discussion” section, we decided to address the critical issue only in the “Strengths and limitations” paragraph of the “Discussion” section.

9) Discussion, fourth paragraph. You cite some references (16–18) that support the specialist management of AMI. Why did you not verify this on your own data? See the point below for further considerations. 10) Discussion, fourth paragraph. I am not one hundred percent sure that including the type of ward in the model would lead to an over-adjustment bias. This variable is a proxy for the setting of AMI onset, but is also a proxy for many potential aspects of care that have an impact on medication adherence. These are, for instance, cardiology follow-up visits and enrollment in post-AMI care pathways. By showing that the lower adherence of IH-AMI patients is largely or partly explained by the ward of discharge, you would be able to discuss aspects of care that are very important to patients and stakeholders. However, if you really think that the type of ward should not be included in the model, I invite you to provide more convincing arguments (is it an intermediate variable or descending proxy? why does this not apply to the other variables?). In this case, you should also remove “discharge ward” from the second paragraph of the Statistical analysis section.

We thank the reviewer for bringing out this issue. Honestly, we have verified the impact of the type of discharge ward on the adherence to evidence-based medications. 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). We have “deliberately” decided not to adjust for discharge ward because we felt it could be an “identikit” for setting of AMI onset. In fact, IH-AMI patients were less likely discharged from specialized wards (48% vs 80%). The effect of setting of AMI-onset could be

partially explained by the effect of discharge ward. If this is the case, then efforts to control for confounding by including discharge ward in our final model may have led to a partial overadjustment of the association between adherence and setting of AMI-onset and thus to an underestimate of the association. According to our findings, IH-AMI patients were 46% less likely to be adherent as compared with OH-AMI patients (OR: 0.54; 95% CI: 0.47-0.62; p-value: <0.001). As might be expected, the association was attenuated after accounting for discharge ward (OR: 0.60; 95% CI: 0.52-0.70; p-value: <0.001).

Last but not least, the authors prefer not to adjust for a variable (discharge ward) that may bring out different care pathways related to the setting of AMI onset. In such manner, we have the possibility to identify weaknesses and improper care in hospital pathways. However, thanks to reviewer's suggestion, the impact of the type of discharge ward on the adherence to E-B drugs expressed as odds ratio, 95% confidence interval and p-value was added in the "Post-AMI adherence to evidence-based medications" paragraph of the "Results" section.

11) General comment. A part of the paper is dedicated to quantifying between-hospital variability using the MOR, but this result is never discussed hereinafter.

According to referee's comment we modified the text in the "Results" and "Discussion" sections. In particular, we revised the text regarding MOR in the "Post-AMI adherence to evidence-based medications" paragraph of the "Results" section and added a sentence about the "between-hospital variability" in the "Adherence to chronic poly-therapy" paragraph of the "Discussion" section.

12) General comment. I suggest that you include the discharge year in your regression model. Post-acute/chronic care and POA coding practices might have evolved between 2012 and 2016.

As suggested by the referee, discharge year was tested as possible determinant of adherence. However, running two different regression models, including or excluding discharge year, the probability of adherence to E-B therapies by setting of AMI onset did not change (OR: 0.54; 95%CI: 0.47-0.62; p-value: <0.001). Therefore, the authors would prefer not to include discharge year in the final model.

In addition, the distribution of adherence to E-B medications and the proportion of IH-AMI patients over 5-year period, is reported in the following table.

Year	Adherence (%)	IH-AMI (%)
2012	59.95	4.15
2013	60.37	4.40
2014	59.32	4.93
2015	59.47	3.68
2016	60.35	3.16

Total	***59.89***	***4.05***

Reviewer 2. Comments to the Author

Bertil Lindahl (Reviewer 2): The main objectives of this study were to measure the adherence to chronic poly-therapy following an AMI; and to identify determinants of adherence to E-B drugs specifically focusing on the potential association between AMI with onset outside hospital and in hospital, respectively (i.e. IH-AMI vs. OHAMI). The authors conclude that pharmacotherapy after AMI is not consistent with clinical guidelines, especially for IH-AMI patients, and that it is possible to identify groups of patients at risk for poor adherence who might benefit from greater medical attention and dedicated health-care interventions. The novelty of the study is the focus on patients with in-hospital onset of AMI. I have several questions and comments.

General:

1. The article would benefit from a language review.

According to reviewer's suggestion, the manuscript has been revised and edited by a native English-speaking colleague.

Methods:

2. The diagnosis code on admission from the RAD register is critical for the definition of IH-AMI and OH-AMI, respectively. Please, explain a little more in detail how the admission diagnosis is made. Many patients at the time of admission to the CCU/ward don't have a definite diagnosis, but is submitted as "suspected AMI", other may be admitted as "unstable angina" which after further testing turned out to meet the criteria for diagnosis of AMI. Can we be sure that the patients classified as IH-AMI really had the onset of the AMI in-hospital?

This is an interesting topic, also raised by the referee #1. Quality of data and accuracy of diagnostic codes are crucial. 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, not applicable, presence cannot be deduced from clinical documentation) 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 ("not applicable" or "presence cannot be deduced from clinical documentation"). In such manner, we should be able to reduce a possible misclassification of exposure due to critical situations, in which patients did not have a definite diagnosis ("suspected AMI") at the time of hospital admission. Moreover, in the Lazio Region, is currently active the Regional Program for Evaluation of Outcomes of Health Care Interventions (P.Re.Val.E.). In Italy, since 2006, this program performs comparative analyses of hospital care, and more than 70 outcome indicators of inpatient care are evaluated [Fusco D, et al. P.Re.Val.E.: outcome research program for the

evaluation of health care quality in Lazio, Italy. BMC Health Serv Res. 2012 Jan 27; 12:25]. The results provided by the P.Re.Val.E. are updated every year and are publicly available. This Program performs continuous audit procedures on the accuracy of ICD diagnostic codes, through a "constant" dialogue between the Department of Epidemiology of the Lazio Region and Lazio hospitals. For all of these reasons, the authors can ensure the reviewer that IH-AMI patients really had an infarction during their hospital stay.

3. The authors wanted to only include incident cases of AMI. Therefore, patients hospitalized for AMI the previous 5 year were excluded. This seems reasonable, but why was patients with a PCI or CABG performed the previous 5 years expected regardless of the underlying diagnosis?

This is a "restriction criteria", in order to obtain a homogeneous population. In fact, with the aim to reducing possible differences within the population regarding to severity of the cardiovascular disease we also excluded patients who performed a PCI or CABG in the 5 years before study entry. These exclusion criteria are widely used in clinical epidemiology and healthcare research.

4. For the definition of adherence to medication the drug dispense registry was used and the MPR was calculated. The drug adherence measured by MPR is dependent on 1) that the drug is prescribed by a physician and 2) that the patient goes to a pharmacy and picks up the prescribed medicine. Do you have any information on to what extent the E-B drugs actually were prescribed at the time of discharge? For how long consumption can a drug be prescribed in Italy? If a drug can be prescribed for 6 months (e.g 180 tablets of betablocker, 1 tabl o.d., will last for the whole 6 month period and per definition give a MPR of 1, even if the patient may have stopped taking the medication after a few weeks). In the discussion section this should be discussed. Is it the adherence to guideline medication by the health care, by the patient, or by a combination that is studied? 6. Please discuss the importance of the "health-care factor" and the "patient factor" for the adherence to the drugs, see point 4 above. MPR will give a over-estimating of the true adherence to the drugs, since we don't know if the patients actually take the drugs.

Drug exposure information was collected from the regional registry of all drugs dispensed by public and private pharmacies and also by hospital pharmacies at discharge. All drugs in this study were included in the patients' healthcare plans and were equally available to all residents, in accordance with the universal healthcare coverage provided to residents of Italy. Moreover, regarding secondary prevention drugs after AMI, it is known that in Italy at the beginning of treatment, the median time between two consecutive prescriptions is generally 30 days. Instead in the "stable phase" of treatment it can rise up to maximum 60 days. Factors contributing to poor medication adherence are myriad and include those that are related to patients, those that are related to physicians and those that are related to health care systems. Because barriers to medication adherence are complex and varied, solutions to improve adherence must be multifactorial [1]. We have "deliberately" decided not to address this issue, because it is not a focus of this research. In fact, our Department of Epidemiology specifically analyzed this topic in a previous study analyzing the trade-off between hospitals of discharge

and community-based providers in determining adherence to chronic polytherapy [2]. However, the authors would like to highlight that, although indirectly, the exposure (onset of AMI) already reflects more an organizational "health-care factor" than an individual clinical "patient-factor". Moreover, we have analyzed the hospital discharge ward as a predictor of adherence. It certainly reflects the final step of the intra-hospital care pathway followed by the patient after an AMI.

[1] Brown, M. T., & Bussell, J. K. (2011). Medication adherence: WHO cares? Mayo Clinic proceedings, 86(4), 304–314.

[2] Di Martino M, Alagna M, Cappai G, Mataloni F, Lallo A, Perucci CA, Davoli M, Fusco D. Adherence to evidence-based drug therapies after myocardial infarction: is geographic variation related to hospital of discharge or primary care providers? A cross-classified multilevel design. BMJ Open. 2016 Apr 4;6(4): e010926.

Regarding to MPR, the authors agree with the referee: the results of adherence based on claims data may be overestimated and should be interpreted with appropriate caution. As suggested, this issue was now discussed in the "Strengths and limitations of the study" paragraph of the "Discussion" section.

Results

5. The study was performed over a 5-year period. Was there any time trend in the adherence to E-B drugs during the period?

As also suggested by Referee#1, discharge year was tested as possible determinant of adherence. However, running two different logistic models, including or excluding discharge year, the probability of adherence to E-B therapies by setting of AMI onset did not change (OR: 0.54; 95%CI: 0.47-0.62; p-value: <0.001). Therefore, there was no evidence of a trend in adherence to E-B medications during the study period. In addition, the distribution of adherence to E-B medications and proportion of IH-AMI patients over 5-year period, is reported in the following table.

Year	Adherence (%)	IH-AMI (%)
2012	59.95	4.15
2013	60.37	4.40
2014	59.32	4.93
2015	59.47	3.68
2016	60.35	3.16
Total	***59.89***	***4.05***

7. Please also discuss the potential effects of using DDD instead of the individual drug dosage for the comparison of MPR between the different drug classes. In the study by Grimmsmann T and Himmel

W (Discrepancies between prescribed and defined daily doses: a matter of patients or drug classes? Eur J Clin Pharmacol. 2011 Aug; 67(8): 847–854.) it was shown that for the “true” betablocker” dosage was significantly lower than the DDD and in contrast significantly higher for ACE-inhibitors.

All the authors agree with this observation. We have now included a sentence addressing this issue and the “link” to suggested bibliographic reference (see reference #33) in the “Strengths and limitations of the study” paragraph of the “Discussion” section. 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.

8. I disagree with the final statement (page 16): “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.” Since, patients with OH-AMI constitute 96% of the AMIs and also has poor drug adherence, although not as poor as IH-AMI, it would be important to focus on improving the adherence regardless of where the AMI starts. However, I agree that patients with IH-AMI deserve further attention.

According to the referee’s comment, we removed the final statement. Moreover, we revised the whole “Conclusions” paragraph of the “Discussion” section in a more explicative manner.

Reviewer 3. Comments to the Author

Maarit Korhonen (Reviewer 3): This study aimed to assess adherence to multiple guideline recommended secondary prevention medications after hospitalization for/including acute myocardial infarction (AMI) and to determine the associations of adherence and the setting of AMI onset (in- vs out of hospital) as well as a few other predictors. The study population consisted of >25 000 hospitalized patients with AMI from one region of Italy in 2012-16. The data came from comprehensive health registers covering the whole population of the region. The evidencebased medications considered were antithrombotics, betablockers, ACE inhibitors/angiotensin receptor blockers (ARB), and statins. Adherence was measured based on prescription claims during a 6-month period after the discharge, using medication possession ratio (MPR). Adherence (MPR >=75% during the 6-month follow-up) to at least 3 medications (“polytherapy”) was the main outcome. In addition to the setting of AMI onset, the following predictors for adherence were considered: age, gender, type of AMI (ST vs non-ST elevation), number of other medications in use prior to hospitalization, and relevant contraindications to at least one of the 4 evidence-based medication categories. In summary, 60% of the patients were deemed adherent to polytherapy. A strong association between the AMI setting and adherence was observed, those with in-hospital AMI being about twice as likely to be nonadherent to polytherapy. The manuscript provides evidence on a previously unidentified predictor of non-adherence to evidence-based medication post-AMI. Another strength is that the authors considered between hospital variation in their data analyses which is often overlooked in similar

studies. However, the clinical consequences of the findings remain somewhat unclear. In addition, I have concerns related to scientific writing. My detailed comments are as follows:

INTRODUCTION

1) The first paragraph of the introduction is to a large extent plagiarized from Bradley et al. Incidence, Risk Factors, and Outcomes Associated With In-Hospital Acute Myocardial Infarction. JAMA Netw Open 2019 Jan; 2(1): e187348 which reads as follows:

"Most studies of acute myocardial infarction (AMI) epidemiology and treatment have focused on patients who experience the onset of AMI outside of the hospital. Insights from these studies have informed risk factors and optimal treatment of AMI, which have led to subsequent reductions in AMI incidence and mortality.1,2 It is increasingly recognized that AMI also occurs among patients already hospitalized for other conditions.3,4 …"

References 1-4 are the same in both papers while the current manuscript does not acknowledge Bradley et al (2019) even as a reference. In the first sentence, the authors of the current manuscript have done some rewording by replacing the expression "patients who experience the onset of AMI outside of the hospital" by "outpatients". However, this seems misleading as the individuals hospitalized for their first AMI are not outpatients (if an outpatient is defined as a patient who receives medical treatment without being admitted to a hospital) Furthermore, the authors state "little is known about the incidence, clinical characteristics and management of patients experiencing in-hospital AMI (IN-AMI)". However, Bradley et al report on these in their paper. In contrast, the current manuscript does not deal with incidence of IN-AMI (see the comment #2) and provides very limited information on IN-AMI patients' clinical characteristics or management other than usage patterns of the 4 guideline-recommended drug groups during the 6 months post-discharge.

Firstly, the authors were very surprised by the term "plagiarism" used by the reviewer. In fact, the objectives of our research and that of Bradley et al. are completely different. Our study aimed to assess adherence to chronic poly-therapy post AMI and to identify predictors of adherence specifically focusing on the potential association between the setting of AMI onset (In versus Out of hospital). By contrast, the objectives of Bradley et al. were to describe the incidence, risk factors and long-term mortality outcomes associated with in-hospital AMI. Therefore, only the setting of AMI onset is "similar" in both papers.

We have deeply revised the "Introduction" section. The expression "outpatients" was deleted, because after reading the reviewer's comment, the authors felt it misleading.
We have included the reference suggested by the reviewer (Bradley et al. 2019) in the "Introduction" section.

2) The word "incidence" is used incorrectly. Incidence of IN-AMI would be calculated as the number of patients with IN-AMI over all individuals hospitalized during the observation period (similarly to Bradley et al.) or as the number of IN-AMI per population with potential exclusions of individuals with prior hospitalizations for related causes from the denominator. Accordingly, in the 2nd pg of the INTRODUCTION, the word "incidence" should be replaced by "onset of AMI".

We agree with the referee, and we replaced "incidence" by "onset of AMI" in the "Introduction" section.

In the DISCUSSION, p. 13, line 23, "incidence" should be replaced e.g. by the following expression "proportion of patients with IN-AMI of all patients with AMI surviving 30 days without rehospitalization after hospital discharge".

We replaced the term "incidence" by "proportion of patients with IH-AMI of all patients with AMI" in the "Clinical characteristics of patients with an IH-AMI" paragraph of the "Discussion" section.

It would be important to cite the Italian guidelines on secondary prevention after AMI and point out that/if they were similar to the international guidelines cited (during the observation period). For example, since 2015 the European Cardiology Society (ECS) guidelines have recommended use of betablockers in post-AMI patients with heart failure and without contraindications only. In any case, it would be important to discuss the differences between the current and prior guidelines in some point of the manuscript. In particular, the role of betablockers in the treatment of post AMI patients has been questioned (e.g. Korhonen MJ, Robinson JG, Annis IE, Hickson RP, Bell JS, Hartikainen J, Fang G. Adherence Tradeoff to Multiple Preventive Therapies and AllCause Mortality After Acute Myocardial Infarction. J Am Coll Cardiol. 2017. 70:1543-54)

The reviewer is right. The role of betablockers in the treatment of post AMI patients now has been addressed in the "Strengths and limitations of the study" paragraph of the "Discussion" section. Anyway, the authors would like to emphasize, how also to take into account the questionable role of betablockers in the secondary prevention of AMI patients, that adherence to chronic poly-therapy was defined as a MPR >=75% for at least three of the four evidence-based drugs, which is a very "unrestricted" definition.

3) References #7-11 mentioned in the 1st sentence of 4th pg do not include information on the association between long-term adherence and survival. E.g. ref #7 does not report anything on long-term adherence to drug therapy nor its benefits after the discharge, the aim being to study "the impact of evidence based medical treatments and coronary revascularisation during or near the event". These authors state "we have no record of ongoing cardioprotective treatment beyond that given at discharge". Ref #9: "We examined the discharge use of medications among 5833 hospital survivors who did not have any contraindications to antiplatelet/anticoagulant, β-blocker, angiotensinconverting enzyme inhibitor, or lipid-modifying therapies." That is, survival benefits of discharge use of these medications were assessed, not those of long-term adherence. References reporting on the association between long-term adherence (6+months) and survival include e.g. ref #13 and the following: Choudhry NK, Glynn RJ, Avorn J, et al. Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. Am Heart J. 2014;167:51–8. e5 Hamood H, Hamood R, Green MS, Almog R. Effect of adherence to evidence-based therapy after acute myocardial infarction on all-cause mortality. Pharmacoepidemiology Drug Saf. 2015;24:1093–104. Korhonen MJ, Robinson JG, Annis IE, Hickson

RP, Bell JS, Hartikainen J, Fang G. Adherence Tradeoff to Multiple Preventive Therapies and All-Cause Mortality After Acute Myocardial Infarction. J Am Coll Cardiol. 2017. 70:1543-54

We thank reviewer for pointing this out and we have now included these three suggested references rather than reference #7, reference #9, and reference #11 in the revised manuscript. Moreover, we have replaced reference #8 and reference #10, respectively by the studies of Mathews et al. (Hospital Variation in Adherence Rates to Secondary Prevention Medications and the Implications on Quality. Circulation. 2018 May 15;137(20):2128-2138) and Gislason et al. (Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. Eur Heart J. 2006 May;27(10):1153-8).

4) Please add references to the 1st sentence of 5th pg to support your statement that substantial variation in AMI treatment exists between hospitals. In addition, the information in the 5th paragraph could be preferably presented after the main objectives.

The fourth paragraph of the "Introduction" section was deleted because the authors felt it was too vague and ambiguous.

5) Overall, the introduction is not convincing in making the case for studying the setting of AMI onset as a potential predictor for adherence. What overall is known about predictors of adherence to secondary prevention medications post-AMI and why do the authors think the setting would be of importance (e.g. prior knowledge about the effect of discharge department could be briefly described here)?

We thank the reviewer for bringing out this issue. The authors think that the transition of care from hospital to the community-based setting represents also 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 in several previous studies. Typically, the hospital takes care of patients in the "first stage" 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. Thanks to reviewer's suggestion, we included a sentence addressing this issue in the "Introduction" section.

METHODS

Data sources

6) The last sentence of the 3rd pg (p. 6, lines 45-49) is unclear: Should patient's severity be severity of patient's condition? Are some words missing from the last part of the sentence "it be able to support …". Please clarify or delete.

Responding to the reviewer's comment, we replaced the term "patient's severity" with "severity of patient's condition" and deleted the last part of the sentence "it be able to support..." because it was misleading.

7) P. 7, line 9: What is the dosage mentioned here? Do you mean strength of a tablet or other unit? It would be important to state here that no information on dosage instructions are available in the data source.

Our pharmaceutical database does not contain information on daily doses prescribed to individual patients and adherence to drug treatment was estimated based on DDDs, used as the dosage assumption. This issue was discussed in the "Strengths and limitations of the study" paragraph of the "Discussion" section.

8) Is there any information on discharge destination (home vs nursing home/assisted care facility)? This information would be important as individuals discharged to nursing homes are likely to be frailer and have lower life-expectancy than those discharged to their homes. In nursing homes or residential care settings individuals are not necessarily responsible for administering their medications and these facilities may even have hospital admission avoidance or deprescribing programs in place. If patients with IH-AMI were more likely to be discharged to nursing homes or similar settings, they may represent a different subset with different goals of care compared to the rest of the post-AMI patients.

The availability of information about discharge destination (home vs nursing home/assisted care facility) would certainly be very useful. Unfortunately, this information was not available from our regional health information systems, so such assessments were not done.

Setting and study cohort

9) What was the rationale for restricting the study cohort to incident cases of AMI?

Incident cases of AMI were defined as no hospitalizations for AMI or related causes in the five years before index admission. This definition ensures that all patients are homogenous with respect to the beginning of the follow-up. Moreover, incident cases reflect the burden of coronary risk factors in the population at large [1], whereas recurrences are further influenced by the quality of coronary care during the acute phase of the incident event and secondary prevention [2].

[1] Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F. et al. Lanasffect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364:937–52

[2] Kangovi S, Grande D. Hospital readmissions-not just a measure of quality. JAMA. 2011; 306:1796–7.

Patient characteristics

10) What is health ticket exemption mentioned on p. 8, lines 30-31? Was there any information on outpatient diagnoses of e.g. asthma? Presence of asthma is likely to be misclassified (underestimated) when relying on hospitalizations or emergency room visits as the information source.

Prescription fees (named "ticket") are applied for particular categories of people, including chronically ill patients (e.g. asthma), people with rare disease and disabled people. Relying also on this additional source of data we should be able to avoid underestimation of asthma diagnosis identified using only hospitalizations or emergency room visits.

Definition of exposure and outcome

11) It seems that the outcome is a mixture of prescriber's adherence to guidelines and patient's refill adherence.

The referee's interpretation is right. The low adherence to treatments is a multidimensional problem determined by the interaction of patient-related factors, physician-related factors, and health system-related factors. Because barriers to medication adherence are complex and varied, solutions to improve adherence must be multifactorial [1]. The multifactorial nature of poor medication adherence implies that only a sustained, coordinated effort will ensure optimal medication adherence and realization of the full benefits of current therapies. In addition, the authors would like to highlight that, although indirectly, the exposure (onset of AMI) certainly reflects the intra-hospital care pathway followed by the patient after an AMI.

[1] Brown, M. T., & Bussell, J. K. (2011). Medication adherence: WHO cares? Mayo Clinic proceedings, 86(4), 304–314.

12) How common is in this health system that patients fill their prescriptions already at the hospital pharmacy on their way home? How long is a prescription valid (or was during the observation period)? Do reimbursement rules restrict the days' supply dispensed per each transaction. In many countries, only a 1- month supply is reimbursed while e.g. in Finland a maximum of 3 months' supply can be reimbursed per transaction. If patients had filled prescriptions for extended periods of time prior to index hospitalization, they may have had E-B medications on hand when discharged from hospital. Ignoring those unused tablets available to the patient at discharge may have led to underestimation of adherence. Could authors comment on this?

Drug exposure information was collected from the regional registry of all drugs dispensed by public and private pharmacies and also by hospital pharmacies at discharge. All drugs in this study were included in the patients' healthcare plans and were equally available to all residents, in accordance with the universal healthcare coverage provided to residents of Italy. Moreover, regarding secondary prevention drugs after AMI, it is known that in Italy at the beginning of treatment, the median time between two consecutive prescriptions is generally 30 days. Instead in the "stable phase" of treatment it can rise up to maximum 60 days.

Regarding the issue of unused medications, the referee is right. Potential unused tablets related to prescriptions prior to index hospitalization were not included in the calculation of adherence. However, during the 6 months preceding start of follow-up, information on the use of all E-B drugs was collected and it was used as potential confounding factor in order to adjust comparisons for "previous use of E-B drugs". A significantly higher adherence to poly-therapy was observed amongst patients already taking E-B medications in the 6 months prior index admission (OR: 1.57; 95% CI: 1.47-1.67; p-value: <0.001).

13) Add reference to the WHO ATC/DDD classification system and specify which year's version was used.

As suggest by the reviewer, a reference was added to the WHO ATC/DDD classification system (References section, reference #32).

14) Were there any combination products of statins (C10B) available in Italy during the study years?

In our claims data, during the study period was available only the following drugs combination: simvastatin and ezetimibe (ATC code: C10BA02). However, the consultant cardiologists in our practice prefer not to recommend this combination therapy (with a statin plus ezetimibe) in the secondary prevention post AMI. Possible use should be limited to cases where LDL cholesterol goal is unmet with statin therapy alone. Anyway, in response to reviewer's comment, we tried to add this drugs combination to measure adherence to chronic poly-therapy, as a sort of sensitivity analysis. However, even if we had considered this class of drug in our analysis, the adherence results would be the same. Hence, this drug category would not in fact lead to changes in the adherence to E-B therapies.

Statistical analyses

15) While multilevel modeling is a clear strength of this study, use of logistic regression model for measuring the association between the exposure(s) and outcome is not optimal. The period over which adherence was measured varies from 30 days up to 180 days. Those patients with IN-AMI have high mortality (up to 60% at 1 year according to Bradley et al. 2019). Their shorter follow-up may reflect lower life-expectancy and different goals of care – which may be a more important reason for lower adherence than the setting of AMI.

The authors do not fully understand this question. Firstly, the results come from Bradley's study cannot be generalizable to our manuscript for several of reasons before anything else due to differences in the organization of national health care services. The same Bradley writes as follows:" Limitations of our study include the VA health care setting, which reflects an older male population and may limit generalizability. Furthermore, our case-control study was restricted to patients aged 50 years and older with in-hospital AMI more than 24 hours after admission and excluded postsurgical patients, which also limits generalizability of our findings to medical admissions in older patients". As previously stated, our manuscript and Bradley's paper are completely different. Secondly, MPR allows to calculate adherence

considering different individual follow-up periods. In our study, individual follow-up started the same date of hospital discharge from the index hospitalization. The end of the observation period was defined as either the end of 6-month follow-up, the time of death or the date of all-cause hospitalization, whichever came first. The authors would like to emphasize that also information on drugs dispensed by hospital pharmacies at discharge was available from our regional drug registry and it was used to calculate adherence to poly-therapy. Moreover, patients who died o received an outpatient regimen for less than 30 days were excluded, in order to allow a long enough time for consistently estimating the adherence to polytherapy. To highlight the "goodness" of our methodology, a comparison between the follow-up times of IH-AMI versus OH-AMI patients was presented: (IH-AMI: mean/median follow-up: 151/180 days VERSUS OH-AMI: mean/median follow-up: 162/180 days). Such a small difference cannot reflect a lower life-expectancy and different goals of care for IH-AMI patients, as supposed by the reviewer.

RESULTS

16) The authors seem to have information on length of the index hospital stay. Its mean/median should be reported for those with IN and OH-AMI.

Following the reviewer's suggestion, we reported the length of the index hospital stay separately for IH-AMI and OH-AMI patients. As expected, the length of the index hospital stay was slightly longer for patients with in-hospital-onset AMI (median: 8 days) than for OH-AMI patients (median: 6 days).

17) For the reasons listed in comment #15, the mean/median follow-up times should be presented for all patients and those with IN and OH-AMI separately.

As reported in answer to comment #15, a comparison between the follow-up times of IH-AMI versus OH-AMI patients was presented: (IH-AMI: mean/median follow-up: 151/180 days VERSUS OH-AMI: mean/median follow-up: 162/180 days).

18) It would be important to report how many patients filled at least 1 prescription for each drug category. Some previous studies on adherence have restricted their study populations to those with at least one fill of each E-B medication (initiators) within a month post-discharge (e.g. Korhonen et al. 2017). In addition, these rates would more closely reflect prescriber's adherence to guidelines than the 6-month adherence.

As suggested by the referee, the number and percentage of patients who filled at least one prescription for each evidence-based drug category, during the 6-month follow-up, is reported in the following table.

E-B drug medication	**At least 1 prescription during follow-up N (%)**
β-Blockers	20 450 (79%)

ACEI/ARBs	20 474 (79%)
Antithrombotics	22 030 (86%)
Statins	22 834 (89%)

In addition, patients who do not fill any prescription for all 4 E-B medications are only 440 (1.7%). The authors would like to emphasize that they are not interested in evaluating prescriber's adherence to guidelines, seeing that our definition of adherence to treatments is a mix of prescriber's adherence and patient's refill adherence. As previously highlighted in the answer to comment #11, the low adherence to treatments is a multidimensional problem determined by the interaction of patient-related factors, physician-related factors, and health system-related factors. Finally, we are not interested to restrict our study population to patients with at least one fill of each E-B drug ("initiators"), because in Italy also information about patients without prescription is "informative" and contribute to the definition of non-adherence to chronic polytherapy.

19) Adherence to each drug category by the setting of AMI onset should be added to Table 2.

As suggested by the reviewer, the adherence to each drug category by the setting of AMI onset, is reported in the following table.

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

IH-AMI patients showed a significantly lower medication adherence for three of four E-B drugs, i.e., statins, antithrombotics and ACEI/ARBs (20, 19 and 15 percentage points lower than OH-AMI, respectively). This "gap" was less significant for Beta-blockers (2 percentage points lower than OH-AMI patients). According to reviewer's suggestion, we added this information in the "Post AMI adherence to evidence-based medications" paragraph of the "Results" section.

20) If it is possible that in the Italian system patients may have had large quantities of unused tablets on hand at the time of hospital discharge, a sensitivity analysis which takes these into account should be conducted.

As previously mentioned in the answer to comment #12, drug exposure information was collected from the regional registry of all drugs dispensed by public and private pharmacies and also by hospital pharmacies at discharge. All drugs in this study were included in the

patients' healthcare plans and were equally available to all residents, in accordance with the universal healthcare coverage provided to residents of Italy. Moreover, regarding secondary prevention drugs after AMI, it is known that in Italy at the beginning of treatment, the median time between two consecutive prescriptions is generally 30 days. Instead in the "stable phase" of treatment it can rise up to maximum 60 days. The referee is right. Potential unused tablets related to prescriptions prior to index hospitalization were not included in the calculation of adherence. However, during the 6 months preceding start of follow-up, information was collected on the use of all E-B drugs and was used as potential confounding factor in order to adjust comparisons for "previous use of E-B drugs". Strikingly, a significantly higher adherence to poly-therapy was observed amongst patients already taking E-B medications in the 6 months prior index admission (OR: 1.57; 95% CI: 1.47-1.67; p-value: <0.001).

DISCUSSION

21) On p. 12, line 37, the authors state that their findings in terms of differences in characteristics between IN and OH-AMI patients accord with those by Zahn et al. However, this is only partly true as in the study by Zahn et al (ref #30) patients with INAMI were LESS likely to have chronic obstructive lung disease and less likely to have used aspirin, betablockers and ACE inhibitors than those with OH-AMI.

The comparisons stated by the reviewer are quite misleading. First, IH-AMI patients had the same change of having chronic obstructive lung disease as OH-AMI in the study by Zahn et al (3.7% vs. 3.8%; OR: 0.98; 95% CI:0.57-1.67). Moreover, in our study we did not collect information about chronic obstructive lung disease, but only about asthma diagnosis. Second, IH-AMI patients were more frequently treated with E-B drugs in the 6 months prior to the index hospitalization, according our findings. By contrast, patients with an in-hospital AMI were less often treated with beta-blockers, as well as with heparin, ACE inhibitors and aspirin during first 48 hours after hospitalization. Anyway, we replaced the sentence "These findings are concordant..." by "Much of these findings are concordant…" in the revised text.

22) In the 2nd pg, lines 48-60, the authors discuss the lower prevalence of adherence among patients with IN-AMI and reasons for this. Discussion on potential differences in lifeexpectancy (reflected e.g. by the follow-up times. In case other diagnoses associated with the hospital stay were available, they could clarify this issue too) and goals of care should be added. Could IN-AMI just be a proxy for frailty?

For the reasons listed in answer to comment #15, the authors absolutely do not believe that IH-AMI can be a proxy for frailty as defined by the referee. In fact, there are no differences in the follow-up times (same median time) between IH-AMI and OH-AMI patients. Therefore, this result cannot reflect a lower life-expectancy and different goals of care for IH-AMI patients, as supposed by the reviewer.

23) Lines 53-54: “Another possible explanation is that, given the often complex and atypical presentations of cardiac disease in patients with other significant comorbidities.” – incomplete sentence?

We thank the reviewer for bringing out this issue. We decided to remove this incomplete sentence because it was too vague and ambiguous.

24) Under the heading Adherence to chronic poly-therapy, the authors seem to focus on underprescribing of evidence-based therapies, yet their outcome is adherence measured by MPR over a 6-month period. This measure is likely to mix prescriber’s decisions with patient’s/carer’s decisions.

The referee’s interpretation is right, as previously highlighted in the answer to comment #11, the low adherence to treatments is a multidimensional problem determined by the interaction of patient-related factors, physician-related factors, and health system-related factors. Because barriers to medication adherence are complex and varied, solutions to improve adherence must be multifactorial [1]. The multifactorial nature of poor medication adherence implies that only a sustained, coordinated effort will ensure optimal medication adherence and realization of the full benefits of current therapies. In addition, the authors would like to highlight that, although indirectly, the exposure (onset of AMI) certainly reflects the intra-hospital care pathway followed by the patient after an AMI.

[1] Brown, M. T., & Bussell, J. K. (2011). Medication adherence: WHO cares? Mayo Clinic proceedings, 86(4), 304–314.

25) The authors discuss gender differences in adherence and state that women are still considered at lower risk of AMI - this is counterintuitive as all patients in this study had an AMI.

We agree with the referee and to avoid confusion, we deleted the sentence in the revised manuscript.

26) Overall, specific references should be added to the sentences stating what has been found in prior studies, e.g. to the statement that cognitive disorders etc. have been associated with lower adherence.

As suggest by the reviewer, a bibliographic reference was added to this sentence (References section, reference #28).

27) Is the expression “inertial effect” authors’ own - if not a reference is needed. It is not quite clear what authors mean by this effect here.

Yes, the expression “inertial effect” is a definition given by the authors. We mean that patients used to take E-B drugs before AMI, generally in order to control individual risk factors such as high arterial blood pressure or high serum cholesterol, are more likely to be adherent to therapies after AMI (when the control of risk factors is even more important) since these patients had acquired a sort of “habit” to the chronic intake of these drugs.

Strengths and limitations

28) Defined daily dose (DDD) is not a necessarily useful tool for estimating the prescribed daily dose of an individual drug when measuring adherence. As the prescribed daily doses are likely to vary across populations, the results from different studies are likely to be biased but not to the same extent; therefore, comparison of the results on adherence measured using DDD from different studies is not easy either. I suggest that the author delete the first part of the sentence "Although this is a useful instrument for comparing the results from different studies" and just state that misclassification of adherence may have occurred because the dosage instructions were not known and the defined daily doses were used as the dosage assumption.

As suggest by the reviewer, we revised the sentence in the "Strengths and limitations of the study" paragraph of the "Discussion" section.

29) Another limitation to the study is that it is not known whether it was the physician's or patient's/carer's decision not to adhere to the guideline-recommended drug therapy. This is an important limitation as it is difficult to say who should be the target of the potential adherence intervention based on the results of this study.

We respectfully disagree with the reviewer. From our standpoint, as repeatedly stressed, all these factors (physician's and patient's decision) played an important role in the definition of adherence to E-B therapies. Actually, according our findings, it is not possible to quantify how much of the 'distance from clinical guidelines' is attributable to the patient behavior, to the therapeutic approach recommended at hospital discharge or to the primary care providers, but this was not our research's purpose. In fact, our Department of Epidemiology specifically analyzed this topic in a previous study, showing that the adherence to E-B drugs was influenced more by the hospital that discharged the patient than by the primary care providers [1]. Our main goal was to measure the associations of adherence to chronic poly-therapy post AMI and the setting of AMI onset to shed light on a previously unidentified subgroups of patients at risk for poor adherence (IH-AMI patients), who might benefit from greater medical attention and dedicated health-care interventions. 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. The last part of the sentence was added in the "Conclusions" paragraph of the "Discussion" section to clarify this topic.

[1] Di Martino M, Alagna M, Cappai G, Mataloni F, Lallo A, Perucci CA, Davoli M, Fusco D. Adherence to evidence-based drug therapies after myocardial infarction: is geographic variation related to hospital of discharge or primary care providers? A cross-classified multilevel design. BMJ Open. 2016 Apr 4;6(4): e010926.

ABSTRACT should be revised to reflect the changes (e.g. wording) in other parts of the manuscript.

The abstract has been deeply revised.

Minor issues Reference #15 is followed by #19 in the text, #16-18 are mentioned after #24.

The sequence of the references has been modified.

VERSION 2 – REVIEW

REVIEWER	Jacopo Lenzi Alma Mater Studiorum - University of Bologna, Italy
REVIEW RETURNED	05-Nov-2020

GENERAL COMMENTS	The authors did a good job addressing my comments. Well done!

REVIEWER	Bertil Lindahl Uppsala Clinical Research Center
REVIEW RETURNED	13-Nov-2020

GENERAL COMMENTS	The paper has been extensively revised and authors have responded to most issues raised by the reviewers. I have some remaining questions and comments. Methods: 1. The diagnosis code on admission from the RAD register is critical for the definition of IH-AMI and OH-AMI, respectively. The authors have tried to explain how this was done in more detail in the response. However, I still not understand how a patient with an admission diagnosis of e.g. unstable angina, in whom the diagnosis of AMI after could be confirmed after the admission, have been classified. Furthermore, how the classification of IH-AMI and OH-AMI was done must also be described in more detail in the manuscript, not only for the reviewers. 2. The introduction has been extensively rewritten (and improved). However, the text in the last paragraph of the introduction (page 7, line 18-28) is almost identically repeated in the discussion, page 15, and again under “Strengths and limitations of the study”, page 17. It can be omitted from the introduction.

REVIEWER	Maarit Korhonen University of Turku, Finland
REVIEW RETURNED	20-Nov-2020

GENERAL COMMENTS	The authors have adequately addressed my concerns. I specifically appreciate that they have changed the wording and expressions of the first paragraph of the introduction which, in my opinion, too closely resembled the text in a paper by Bradley.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1. Comments to the Author

Jacopo Lenzi (Reviewer 1): The authors did a good job addressing my comments. Well done!

Reviewer 2. Comments to the Author

Bertil Lindahl (Reviewer 2): The paper has been extensively revised and authors have responded to most issues raised by the reviewers. I have some remaining questions and comments.

Methods:

1. The diagnosis code on admission from the RAD register is critical for the definition of IH-AMI and OH-AMI, respectively. The authors have tried to explain how this was done in more detail in the response. However, I still not understand how a patient with an admission diagnosis of e.g. unstable angina, in whom the diagnosis of AMI after could be confirmed after the admission, have been classified. Furthermore, how the classification of IH-AMI and OH-AMI was done must also be described in more detail in the manuscript, not only for the reviewers.

--> The reviewer is right: a more detailed explanation on the classification of IH-AMI and OH-AMI patients has been added in the “Setting and study cohort” paragraph of the “Methods” section.

To address the concern raised by the reviewer, the authors would like to emphasize that the additional information regarding AMI diagnostic codes at the time of hospital presentation, retrieved using the RAD Information System, are inserted into the RAD forms only at the time of patient’s hospital discharge, when the diagnostic and therapeutic care pathways are clearly defined. This last sentence was added in the “Data sources” paragraph of the “Methods” section to clarify this topic.

2. The introduction has been extensively rewritten (and improved). However, the text in the last paragraph of the introduction (page 7, line 18-28) is almost identically repeated in the discussion, page 15, and again under “Strengths and limitations of the study”, page 17. It can be omitted from the introduction.

--> According to reviewer’s suggestion, the text in the last paragraph of the “Introduction” section was removed.

Reviewer 3. Comments to the Author

Maarit Korhonen (Reviewer 3): The authors have adequately addressed my concerns. I specifically appreciate that they have changed the wording and expressions of the first paragraph of the introduction which, in my opinion, too closely resembled the text in a paper by Bradley.