PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Survival prospects after acute myocardial infarction in the United Kingdom: a matched cohort study 1987-2011
AUTHORS	Gitsels, Lisanne; Kulinskaya, Elena; Steel, Nicholas

VERSION 1 - REVIEW

REVIEWER	Etienne PUYMIRAT European Hospital of Georges Pompidou Departement of Cardiology Paris, France
REVIEW RETURNED	19-Aug-2016

GENERAL COMMENTS	The authors assessed the hazard of mortality and the effects of recommended treatments associated with a history of acute myocardial infarction (AMI) at keys ages (60, 65, 70, 75 years) between 1987 and 2011 in UK residents. Patients were matched on sex, year of birth, and general practice to three controls groups each (no ischemic heart disease, angina, multiples AMIs). The authors showed the evolution of clinical practices in UK over a 24-years period. In addition, they demonstrated that survival was better in patients who had coronary revascularization or were prescribed statins or beta-blockers, but worse in those prescribed aspirin (at older age) or ACE-inhibitors. These data are very interesting. Overall, the draft is well written, analyses are appropriate, and the conclusions reasonable from the data displayed. Comments: 1) In the methods part, data were collected between January 1987 and March 2011 while in the abstract (design) data were collected between January 1988 and March 2011. Please be consistent. 2) The rate of STEMI should be mentioned in the manuscript for each cohort (if available). 3) The rate of percutaneous coronary intervention (PCI) and CABG should be also mentioned in the manuscript for each cohort (if available). 4) The hazard of all-causes mortality associated with AMI was calculated by multilevel cox proportional hazard regressions, adjusted for several variables. However, several important variables are missing especially left ventricular function. If available, these data should be included in the final model. 5) The use of a dual antiplatelet therapy (DAPT) after AMI is recommended since several years for 12 months but aspirin is the only antiplatelet therapy (APT) included in the model. This

	represents a major limitation. Clopidogrel (and others APT) should be also included in the model (if applicable). 6) The absence of doses (for medication) is a real limitation and should be mentioned in the limitation part. 7) Recently, In the Pegasus trial (Bonaca MP et al. N Engl J Med 2015), several atherothrombosis risk factors have been used to define a high-risk population of patients with previous AMI. Multivessel CAD seems to be an important variable. In addition the definition of CKD used was different (CrCl <60 mL/min) compared to the present study. This could be briefly discussed in the manuscript. 8) Finally, results related to aspirin are strange (in older patients). The authors should be more moderate (abstract and conclusions) because there is no rational explanation.

REVIEWER	Gunilla Journath Department of Medicine, Karolinska Institutet, Cardiology Unit, Karolinska University Hospital, Solna, Sweden Financial disclosures: GJ has received consultant fee from Amgen A
REVIEW RETURNED	30-Aug-2016

GENERAL COMMENTS	This is a well written manuscript and quite easy to follow. Please check tempus all through the manuscript. Why did the investigators not use a propensity score matched control group?

REVIEWER	Freisinger, Eva Department of Cardiovascular Medicine University Hospital Muenster, Muenster, Germany
REVIEW RETURNED	28-Sep-2016

GENERAL COMMENTS	The authors aim to investigate the mortality after acute myocardial infarction (AMI) in a real-world scenario based on a secondary data analysis derived from general practice patient files. The cohort of AMI patients was compared to a matched cohort with same sex and age. The data analysis covers a time period from 1987-2011. Strength of the study is large size, longitudinal character, very detailed patient information with regard to co-morbidities and medication, and good statistical approach. Major limitation of the study design itself is that the available detailedness of data is not utilized, but patients with a great variety of diagnoses (STEMI/NSTEMI/mixed co-diagnoses and risk constellations), procedures (endovascular/surgical revascularization/lysis) and therapy at very different time periods (involving important and partially dramatic changes in recommended and available therapy, diagnostics, encoding behaviour, ..) are all lumped together resulting in one end-point (all-cause death). Further, the observational data do not allow causal conclusions as drawn by the authors at many text passages and data interpretation needs major revision from a clinical point of view. ----------

	Objective: The addressed question is interesting, yet will not provide profound new information since nation-wide data on AMI mortality, also based on routine data, has been published previously. mortality = all-cause mortality? - Your detailed patient information would allow to address a lot more sophisticated and interesting questions that would probably be of higher value for clinicians and health care providers. Methods/ Setting and Participants: major points It is a major drawback in the design of the analysis that the primary diagnosis of „acute myocardial infarction“ is not further specified into STEMI and NSTEMI! From a clinical point of view, both entities of AMI differ significantly in terms of patient's characteristics, recommended treatment strategies, and prognosis! Further, the diagnosis of STEMI is more „watertight“, whereas the diagnosis of NSTEMI, particularly before the invention of the high-sensitive-Troponin testing, underlies a certain deviation.. Please consider with regard to the long time period (1987-2011) that a) diagnostic criteria for AMI changed b) diagnostics improved (e.g. hs Trop) c) therapeutic approach significantly changed (eg invention of DE-stenting, decreased importance of lysis therapy, new anticoagulants ..) with dramatic impact on recommended practice and patient's outcome (eg bleeding risk, mortality) d) take possible incentive set by the reimbursement system into account for the AMI diagnosis (particularly of NSTEMI) >>>>> I would strongly advise the authors to confine their analysis on patients with STEMI (or at least to make two subgroups: STEMI and NSTEMI which should be analyzed separately). Futher, I would recommend to limit the data to a time period of the last ten years to reduce the high impact of the afore mentioned changes over the past decades. With regard to your high patient number, this will still leave you with a great size of the cohort. <<<<<< Control cohorts: It is not clear how control patients have been selected. Apart from the same age and sex, do these patients have a comparable cardiovascular risk profile? From the baseline table 1 it is evident, that only 5-20% have „other cardiovascular conditions“ (detailed definition??) however, do all of these control patients have an indication for the evaluated medication (aspirin, ACE inhibitors, statins etc)?? Baseline characteristics: ratio of patients with heart failure (5-12%), chronic kidney disease (0-10%), diabetes (11-20%) seems very low given the fact that these AMI patients include those with recurrent infarction, NSTEMI, age >60years .. please explain! (encoding accuracy, patient cohort, diagnostic accuracy particularly in the early recruiting period.. CKD: why only end-stage CKD was considered?!) Table 2: Percentage of coronary revascularization in AMI patients is very low, given PCI first-line recommended therapy! Also, medication with aspirin, statins etc are class 1A guideline recommendations, thus 100% of AMI patients should receive this. This needs explanation. I wonder what these statistics would look like if the authors would confine their analysis on only STEMI patients in the past decade.

	minor points: data base general practice: AMI patients should see a cardiologist on a regular basis, data from the cardiologist may be more comprehensive and valid than from the general practice.. AMI diagnosis includes patients with „single AMI or multiple AMI“ : these patients may significantly differ in their cardiovascular risk / mortality risk! Why not chose only patients with first AMI, recurrent AMI would be an important end-point to consider (MACE).. - Subject matter/ Introduction and Discussion: - >>>>> I think the manuscript paragraphs on the medical background as well as data interpretation would improve a lot if the authors would consult a cardiologist/ expert clinician to discuss their findings.<<<<<<<<< ::: e.g. Introduction „..better coverage of patients with AMI than hospitals and registers, because it includes those with less severe AMI who did not have to go to the hospital,..“ An acute myocardial infarction is a life-threatening condition that is never recommended to be treated in an ambulatory setting. - „This study found that the lower uptake of coronary revascularisation by women could not be explained by age, diabetes, or deprivation, as suggested by a previous study,10 which suggests that there might be sex discrimination in access to surgery.“ Coronary revascularisation is mainly an endovascular catheter based procedure (PCI), and only to a smaller part coronary artery bypass surgery (CABG). However, patients who need CABG not only differ in terms of the distribution pattern of their coronary artery lesions but also surgery itself has a higher periprocedural risk for complications and death compared to PCI. - in terms of medication (e.g. findings on the „hazardous effects of ACE-inhibitors and aspirin on survival“), the general AMI patient cohort seems severely under-treated with regard to current international guideline recommendations. As regards content, the data analysis may show associations between the intake of certain medication and patient’s outcome, however this reflects a selection of (high-risk) patients and does not necessarily reflect a causal link! >>>> manuscript preparation: - the manuscript is way too long!! headline: 1987-2011 abstract: 1988 - 2011 Study design: „The rationale behind matching cases to controls, was to create a more balanced dataset for the exposure was a relatively rare event.“ I do not understand the sense of this sentence. data interpretation in the results part -> move to the discussion and limitation.

REVIEWER	Terje P. Hagen University of Oslo, Norway
REVIEW RETURNED	05-Oct-2016

GENERAL COMMENTS	GENERAL COMMENTS The topic is of interest, the methods are sound and well documented and most of the results reasonable. Main strength is the study design with matched cohorts. The main problem is that the paper is too short in terms of supplying the reader with sufficient overview of the institutional context, including how AMI is diagnosed in primary care. DETAILED COMMENTS 1. AMI is defined from symptoms, ECG abnormalities and cardiac enzymes (troponins). In most European countries both symptoms and ECG can be detected in primary care while troponin test are done in hospitals. How is this in the UK? If the "final" diagnosis is set in hospitals why are there differences in registered cases between hospital registers and primary care records? 2. Survival following AMI is dependent upon type of AMI where STEMIs in general have higher mortality then non-STEMIS. It is not clear how this is handled in the study. Does the data include information of type of AMI at all? 3. The lower uptake of PCI/CABG among women can be related to more non-STEMIs among females. 4. If type of AMI is unknown it is hard to see how type of treatment can be evaluated since treatment will depend on type of AMI. Matching will probably not solve the problem. 5. The dependent variable is time to death. We need the exact definition. Is time from death calculated from onset of the AMI, from treatment in primary care (index day) or from a possible discharge date from a hospital or a GP setting. 6. The final model includes several covariates including medication use. Are use of medication only registered after the treatment episode or are (some) of the medication in use also before the onset of the disease and start of the treatment? If data on some of the covariates are registered before the onset of the AMI they probably will work more like risk adjusters than treatment. This needs clarification. 7. On the end of page 4 the term "ward" turns up. What is this and how does a ward relate to the general practice? A short introduction to the institutional setting is needed, including a description of typical pathway for AMI patients.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Etienne PUYMIRAT
Institution and Country: European Hospital of Georges Pompidou, Department of Cardiology, Paris, France Competing Interests: None declared

The authors assessed the hazard of mortality and the effects of recommended treatments associated

with a history of acute myocardial infarction (AMI) at keys ages (60, 65, 70, 75 years) between 1987 and 2011 in UK residents. Patients were matched on sex, year of birth, and general practice to three controls groups each (no ischemic heart disease, angina, multiples AMIs).

The authors showed the evolution of clinical practices in UK over a 24-years period. In addition, they demonstrated that survival was better in patients who had coronary revascularization or were prescribed statins or beta-blockers, but worse in those prescribed aspirin (at older age) or ACE-inhibitors.

These data are very interesting.

Overall, the draft is well written, analyses are appropriate, and the conclusions reasonable from the data displayed.

Comments:
1) In the methods part, data were collected between January 1987 and March 2011 while in the abstract (design) data were collected between January 1988 and March 2011. Please be consistent.

We thank the reviewer for the comment and we corrected the entry year in the abstract.

2) The rate of STEMI should be mentioned in the manuscript for each cohort (if available).

This information is not available in The Health Improvement Network (THIN) database, which is used for this study. THIN and GPRD (General Practice Research Database) include primary care records from approximately 600 practices that use the Vision clinical system, of which 60% of practices are the same (Reeves et al., 2014). Even though these databases include different general practices and patients, the estimated incidence, prevalence, and mortality rates are similar across the databases and with national surveys when adjusted for sex, age, and deprivation (idem.). A study by Herrett et al. (2013a) linked information from the Myocardial Ischaemia National Audit Project (MINAP) and the GPRD and found that 46% of AMIs were ST-elevated in England and Wales in 2003-2008. This information was added to the manuscript:
The primary exposure was AMI. Multiple events were required to be separated by 30 days. Information on the type of AMI was not available. However, a study that linked information from the Myocardial Ischaemia National Audit Project (MINAP) and the General Practice Research Database (GPRD), which has 60% of practices in overlap with THIN, found that 46% of AMIs were ST-elevated in England and Wales in 2003-2008 (Herrett et al., 2013a).

3) The rate of percutaneous coronary intervention (PCI) and CABG should be also mentioned in the manuscript for each cohort (if available).

In the supplementary file, we included a table on the prevalence of CABG and PCI for each age cohort. The rate across the four age cohorts for CABG and PCI were 16-19% and 3-8%, respectively (see Table 1 at the end of this letter). We included this information in the Results' subsection 'Prevalence of treatment':
In the cohorts studied, the prevalence of coronary revascularisation and drug therapy was higher among patients who had multiple AMIs compared to participants who had a single AMI (Table 2). The rate across the four age cohorts for coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) were 16-19% and 3-8%, respectively (Table A6 in the Online Data Supplements). Men were approximately twice as likely to have had coronary revascularisation as women were, which could not be explained by age, deprivation, or diabetes (Figure A2 and Table A5 in the Online Data Supplements). Men and women were equally likely to be prescribed drugs.

4) The hazard of all-causes mortality associated with AMI was calculated by multilevel cox proportional hazard regressions, adjusted for several variables. However, several important variables are missing especially left ventricular function. If available, these data should be included in the final model.

Severity indicators of AMI, such as left ventricular function, were not included in the survival model. This was because the information would only be available for the cases and not the controls, translating to 75% missing values. Please note that heart failure, which consist of both left and right sided failures, was included in the survival models and thus covered left ventricular failure. The limitation of excluding AMI severity indicators is added to the Discussion's subsection 'Study's strengths and limitations':
Although the major confounders of AMI were adjusted for, there could potentially be some residual confounding by a number of other factors: family history of cardiovascular disease, family history of AMI, psychosocial factors, fruit and vegetable intake, and physical activity. These factors were not adjusted for in the survival models due to the unsystematic or no recording in the medical records. AMI severity indicators, such as left ventricular function, were also not included in the survival models because this information was only available for the cases and not the controls.

5) The use of a dual antiplatelet therapy (DAPT) after AMI is recommended since several years for 12 months but aspirin is the only antiplatelet therapy (APT) included in the model. This represents a major limitation. Clopidogrel (and others APT) should be also included in the model (if applicable).

The treatment investigated was based on the UK National Institute of Health and Care Excellence (NICE) recommended first line treatment to AMI patients for cardiac rehabilitation and prevention of another AMI during the study period. The recommendation of DAPT was added to the NICE guideline in 2013 (NICE, 2013a). This means that during the study period of 1987-2011, a second antiplatelet agent was not a first line treatment to AMI patients. The prevalence of DAPT in the 60-, 65-, 70-, and 75-year old cohort was 1%, 3%, 6%, and 7%, respectively (see Table 2 at the end of this letter). We included this information in the manuscript:
The treatment investigated was based on the UK National Institute of Health and Care Excellence (NICE) recommended first line treatment to AMI patients during the study period, which includes: coronary revascularisation and prescription of ACE-inhibitors, aspirin, beta blockers, calcium-channel blockers, and statins.21-23 Since 2007, calcium-channel blocker is only recommended to treat hypertension or angina in AMI patients.22-23 Since 2013, dual antiplatelet therapy (DAPT: aspirin plus another antiplatelet agent) are recommend to AMI patients.22-23 Due to the low prevalence of DAPT in the age cohorts, the survival effect of the therapy were not estimated (Table A3 in the Online Data Supplements).

6) The absence of doses (for medication) is a real limitation and should be mentioned in the limitation part.

We thank the reviewer for the comment. This limitation is added to the Discussion's subsection 'Study's strengths and limitations':
Adherence to drug therapy was unknown and therefore the survival prospects associated with prescription of drug therapy might not accurately reflect the effect of the drugs themselves on mortality. Furthermore, no dose-response effect could be estimated as the prescribed doses were not included in the survival models.

7) Recently, In the Pegasus trial (Bonaca MP et al. N Engl J Med 2015), several atherothrombosis risk factors have been used to define a high-risk population of patients with previous AMI. Multivessel CAD seems to be an important variable. In addition the definition of CKD used was different (CrCl <60 mL/min) compared to the present study. This could be briefly discussed in the manuscript.

Multivessel coronary artery disease is a severity indicator of ischaemic heart disease, which is included in the survival model. Please see our response to question 4 regarding severity indicators. We looked into the CKD definition and corrected it to being stage 3 to 5, i.e. CrCl<60mL/min. The Pegasus trial held in the US consisted of a sicker population than the general population in the UK. The prevalences of comorbidities in our age cohorts were similar to the study including individuals of all ages admitted with AMI to hospital in England in 2004-2010 (Smolina et al., 2012b).

8) Finally, results related to aspirin are strange (in older patients). The authors should be more moderate (abstract and conclusions) because there is no rational explanation.

The NICE guideline on secondary prevention of AMI only included one randomised control trial that studied the effect of aspirin compared to placebo on the hazard of all-cause mortality (NICE, 2013b). That study took place in 1972 to 1974 in the United States and included males aged 30 to 64 years with a recent AMI (n=1,529) (Coronary Drug Project, 1980). The study found inconclusive survival benefit associated with aspirin. Our study that takes place in the United Kingdom made use of more recent data with a longer follow-up (1987-2011) of older patients (60, 65, 70, or 75 at baseline) of both sexes (sample sizes across age cohort ranged from 16,744 to 76,392 patients). The NICE guideline reported that aspirin is associated with an increased risk of bleeding, where the risk increases with age (idem). Because elderly are excluded from most clinical trials, it could be that there is no survival benefit of aspirin in the elderly. We included this argument in the Discussion section:
- The findings of this study agree with the clinical evidence reviewed by NICE23 on the effectiveness of statins and calcium-channel blockers, but disagree with the effectiveness of ACE-inhibitors, aspirin, and beta-blockers. […] The NICE review on aspirin only included one study that estimated an inconclusive protective effect of the drug versus placebo on all-cause mortality (NICE, 2013b). That study included men with a recent AMI aged 30-64 in 1972-1974 (Coronary Drug Project, 1980). The current study made use of more recent data with longer follow-up of older patients of both sexes. Aspirin is associated with an increased risk of bleeding, where the risk increases with age (NICE, 2013b). Because elderly are excluded from most clinical trials, the aspirin might actually be harmful in elderly as the findings of the current study suggest.
- This study also found that the prescriptions of aspirin by age 70 or 75 and/or ACE-inhibitor by any age were associated with an increased hazard of mortality.

Reviewer: 2
Reviewer Name: Gunilla Journath
Institution and Country: Department of Medicine, Karolinska Institutet, Cardiology Unit, Karolinska University Hospital, Solna, Sweden Competing Interests: Financial disclosures: GJ has received consultant fee from Amgen AB

This is a well written manuscript and quite easy to follow.
Please check tempus all through the manuscript.
Why did the investigators not use a propensity score matched control group?

We thank the reviewer for the comment. We chose frequency matching with fixed number of controls instead of propensity score matching with variable number of controls because enough controls per case could be matched (in this study 3 controls per case). Moreover, with frequency matching, the controls are representative of the general population when adjusted for sex, age, and deprivation. With propensity score matching, weights would need to be applied to make the controls representative of the general population as with this technique people at high risk of an AMI would be selected as controls.

Reviewer: 3
Reviewer Name: E Freisinger
Institution and Country: Department of Cardiovascular Medicine, University Hospital Muenster, Muenster, Germany Competing Interests: none declared

The authors aim to investigate the mortality after acute myocardial infarction (AMI) in a real-world scenario based on a secondary data analysis derived from general practice patient files. The cohort of AMI patients was compared to a matched cohort with same sex and age. The data analysis covers a time period from 1987-2011.

Strength of the study is large size, longitudinal character, very detailed patient information with regard to co-morbidities and medication, and good statistical approach.
Major limitation of the study design itself is that the available detailedness of data is not utilized, but patients with a great variety of diagnoses (STEMI/NSTEMI/mixed co-diagnoses and risk constellations), procedures (endovascular/surgical revascularization/lysis) and therapy at very different time periods (involving important and partially dramatic changes in recommended and available therapy, diagnostics, encoding behaviour, ..) are all lumped together resulting in one end-point (all-cause death). Further, the observational data do not allow causal conclusions as drawn by the authors at many text passages and data interpretation needs major revision from a clinical point of view.

Objective:
The addressed question is interesting, yet will not provide profound new information since nation-wide data on AMI mortality, also based on routine data, has been published previously.
mortality = all-cause mortality?

We thank the reviewer for the comment. As outlined in the Introduction of the manuscript, national statistics report sex- and age-standardised mortality rates which are likely to underestimate the survival prospects of AMI patients. These patients may be more likely to have comorbidities and an unhealthy lifestyle, which are independent predictors of survival, and so adjustment for these confounders is important.

- Your detailed patient information would allow to address a lot more sophisticated and interesting questions that would probably be of higher value for clinicians and health care providers.

Methods/ Setting and Participants:
major points
It is a major drawback in the design of the analysis that the primary diagnosis of „acute myocardial infarction“ is not further specified into STEMI and NSTEMI! From a clinical point of view, both entities of AMI differ significantly in terms of patient’s characteristics, recommended treatment strategies, and prognosis! Further, the diagnosis of STEMI is more „watertight“, whereas the diagnosis of NSTEMI, particularly before the invention of the high-sensitive-Troponin testing, underlies a certain deviation..

Please see our response to question 2 of reviewer 1.

Please consider with regard to the long time period (1987-2011) that a) diagnostic criteria for AMI changed b) diagnostics improved (e.g. hs Trop) c) therapeutic approach significantly changed (eg invention of DE-stenting, decreased importance of lysis therapy, new anticoagulants ..) with dramatic impact on recommended practice and patient’s outcome (eg bleeding risk, mortality) d) take possible

incentive set by the reimbursement system into account for the AMI diagnosis (particularly of NSTEMI)

We agree with the reviewer that there have been considerable changes in the diagnosis and treatment of AMI (Smolina et al., 2012a). The European Society of Cardiology and the American College of Cardiology introduced a new diagnostic criterion of AMI in 2000 (idem.). The new criterion measures the amount of troponin I or T in a blood sample. The new criterion leads to more diagnoses of AMI and thus also to a higher reported incidence of milder cases. Studies in Denmark (Abildstrom et al, 2005), Finland (Salomaa et al., 2006), Australia (Sanfilippo, 2008), and the United States (Roger et al., 2010) showed that the new criterion affects the incidence rate but not the mortality rate. This is because the new criterion increased the prevalence of AMI in patients aged 70 or older, who have a worse survival rate than younger patients.

In this study, we adjusted for several risk factors, including year of birth category and AMI treatments. Year of birth category should take into account possible advances in medical management over time. Moreover, we specifically tested for and found no interaction between year of birth category and AMI diagnosis and treatments, suggesting that the effect of AMI and its treatments on the hazard of mortality do not vary over time other than the general year of birth cohort effect. In conclusion, we do not share the concern of confounding by time trend.

>>>>> I would strongly advise the authors to confine their analysis on
>>>>> patients with STEMI (or at least to make two subgroups: STEMI and
>>>>> NSTEMI which should be analyzed separately). Futher, I would
>>>>> recommend to limit the data to a time period of the last ten years
>>>>> to reduce the high impact of the afore mentioned changes over the
>>>>> past decades. With regard to your high patient number, this will
>>>>> still leave you with a great size of the cohort. <<<<<<

We run a subset analysis on data from 2001-2011. With data available on patients who were born between 1920 and 1940, this meant that the 60-year old cohort could no longer be studied. The sample sizes of the 65-, 70-, and 75-year old cohorts reduced to 21,696, 49,352, and 58,008 patients, respectively. The estimated hazard ratios on these subsets were slightly lower or higher than the ones estimated on the full cohorts, with overlapping confidence intervals (see Table 3 at the end of this letter). This meant that the conclusions of our study did not change by the subset analysis.

Control cohorts: It is not clear how control patients have been selected. Apart from the same age and sex, do these patients have a comparable cardiovascular risk profile? From the baseline table 1 it is evident, that only 5-20% have „other cardiovascular conditions“ (detailed definition??) however, do all of these control patients have an indication for the evaluated medication (aspirin, ACE inhibitors, statins etc)??

We thank the reviewer for the comment. As outlined in the Methods' section of the manuscript, patients with a history of AMI were selected and each matched to three controls without this history on sex, year of birth category, and general practice. The cases and controls could thus differ in cardiovascular risk profile. Controls could receive similar treatment due to primary or secondary prevention of a cardiac event. The controls are representative of the general population when adjusted for sex, age, and deprivation. Even though the matching did not include cardiovascular risk profile, by adjusting for cardiovascular and non-cardiovascular risk factors, unbiased estimates of survival prospects after AMI diagnosis and treatments could be obtained.

Baseline characteristics: ratio of patients with heart failure (5-12%), chronic kidney disease (0-10%), diabetes (11-20%) seems very low given the fact that these AMI patients include those with recurrent

infarction, NSTEMI, age >60years .. please explain! (encoding accuracy, patient cohort, diagnostic accuracy particularly in the early recruiting period.. CKD: why only end-stage CKD was considered?!) Table 2: Percentage of coronary revascularization in AMI patients is very low, given PCI first-line recommended therapy! Also, medication with aspirin, statins etc are class 1A guideline recommendations, thus 100% of AMI patients should receive this. This needs explanation. I wonder what these statistics would look like if the authors would confine their analysis on only STEMI patients in the past decade.

We thank the reviewer for the comments. We compared the prevalence of risk factors in our age cohorts with individuals of all ages admitted with AMI to hospital in England in 2004-2010, which were studied by Smolina et al. (2012b). They found that 75% of AMI patients had a history of cardiovascular disease, 19% had diabetes, and 5% had chronic kidney disease. This is comparable to our age cohorts in 1987-2011, with the medical records assessed at ages 60, 65, 70, and 75. In our cohorts we do not take into account all types of cardiovascular disease but selected angina, heart failure, and other cardiovascular conditions (valvular heart disease, peripheral vascular disease, and cerebrovascular disease). When combining these specific types, the prevalence in AMI patients for each age cohort is 56%, 60%, 63%, and 68%, respectively for age 60, 65, 70, and 75.

With regards to the low prevalence of treatments in AMI patients, Table 2 provides the average prevalence during 1987-2011. As outlined in the description box of Table 2, the prevalence of treatment by the initial ages increased substantially by calendar year (Figure A1 in the Online Data Supplements). The prescription trends of ACE-inhibitors, aspirin, beta-blockers, and statins are in line with the published results of prescription of evidence-based medications following AMI in primary care in the UK in 1991-2001 (Hardoon et al., 2011). In 2010 almost all AMI patients were prescribed statins (94%) and aspirin (94%), the majority were prescribed ACE-inhibitors (85%) and beta blockers (65%), and a minority underwent coronary revascularisation (38%). The prevalence of revascularisation is higher than the 20% reported by Smolina et al. (2012b) who studied individuals of all ages admitted with AMI to hospital in England in 2004-2010. The lower prevalence reported by Smolina et al. could inter alia be due to the criterion that the surgery had to take place within 30 days after the AMI, which our study does not have. In the Recommendations' subsection of the manuscript, we highlighted that not every AMI survivor received all the first line treatments and suggested that the survival prospects of AMI survivors not receiving these treatments might be improved by such prescriptions or surgery.

minor points:
data base general practice: AMI patients should see a cardiologist on a regular basis, data from the cardiologist may be more comprehensive and valid than from the general practice.

We thank the reviewer for the comment. A study by Herrett et al. (2013b) determined the completeness and diagnostic validity of myocardial infarction recording in primary care, hospital care, disease registry, and national mortality records in England in 2003-2009. The researchers found that risk factors and non-cardiovascular coexisting conditions were similar across patients identified across the four national health record sources.

AMI diagnosis includes patients with „single AMI or multiple AMI" : these patients may significantly differ in their cardiovascular risk / mortality risk! Why not chose only patients with first AMI, recurrent AMI would be an important end-point to consider (MACE)..

We agree with the reviewer that the survival prospects of patients with a single or multiple AMIs differ from each other. That is why we estimated the survival prospects for these patients separately.

Subject matter/ Introduction and Discussion:
- >>>>> I think the manuscript paragraphs on the medical background as well as data interpretation

would improve a lot if the authors would consult a cardiologist/ expert clinician to discuss their findings.<<<<<<<<< :::
e.g. Introduction „..better coverage of patients with AMI than hospitals and registers, because it includes those with less severe AMI who did not have to go to the hospital,..“ An acute myocardial infarction is a life-threatening condition that is never recommended to be treated in an ambulatory setting.

We thank the reviewer for the comment and changed the statement to the following:
Additionally, primary care has a higher prevalence of AMI than hospital care and disease registers because it includes patients who were diagnosed immediately and patients who were not sent to the hospital but were diagnosed in the community later by blood test results (Herrett et al., 2013b).

- „This study found that the lower uptake of coronary revascularisation by women could not be explained by age, diabetes, or deprivation, as suggested by a previous study,10 which suggests that there might be sex discrimination in access to surgery.“ Coronary revascularisation is mainly an endovascular catheter based procedure (PCI), and only to a smaller part coronary artery bypass surgery (CABG). However, patients who need CABG not only differ in terms of the distribution pattern of their coronary artery lesions but also surgery itself has a higher periprocedural risk for complications and death compared to PCI.

We agree with the reviewer that AMI patients differ in needs for surgery, however the study found uptake differences by sex and deprivation. As discussed in the paper, the European Society for Cardiology recognises these differences and advocates equality in treatment (Chieffo et al., 2012).

- in terms of medication (e.g. findings on the „hazardous effects of ACE-inhibitors and aspirin on survival“), the general AMI patient cohort seems severely under-treated with regard to current international guideline recommendations. As regards content, the data analysis may show associations between the intake of certain medication and patient’s outcome, however this reflects a selection of (high-risk) patients and does not necessarily reflect a causal link!

We thank the reviewer for the comment and revised the Discussion’s section with a more cautious conclusion.

>>>> manuscript preparation:
- the manuscript is way too long!!

We reduced the number of words to 4,015, which is approximately the recommended length of 4,000 words set by BMJ Open.

headline: 1987-2011 abstract: 1988 - 2011

We thank the reviewer for the comment and we corrected the entry year in the abstract.

Study design: „The rationale behind matching cases to controls, was to create a more balanced dataset for the exposure was a relatively rare event.“ I do not understand the sense of this sentence.

A more balanced cohort, as created by matching, translates in increased statistical power and efficiency (Greenland & Morgenstern, 1990; Hennekens et al. 1987). In other words, there is more power to identify an effect that truly exists and more optimal use of the data is made as fewer patients are needed for a given result.

Data interpretation in the results part -> move to the discussion and limitation.

We thank the reviewer for the comment and moved any interpretations in the Results' section to the Discussion's section.

Reviewer: 4
Reviewer Name: Terje P. Hagen
Institution and Country: University of Oslo, Norway Competing Interests: None declared

GENERAL COMMENTS
The topic is of interest, the methods are sound and well documented and most of the results reasonable. Main strength is the study design with matched cohorts. The main problem is that the paper is too short in terms of supplying the reader with sufficient overview of the institutional context, including how AMI is diagnosed in primary care.

DETAILED COMMENTS
1. AMI is defined from symptoms, ECG abnormalities and cardiac enzymes (troponins). In most European countries both symptoms and ECG can be detected in primary care while troponin test are done in hospitals. How is this in the UK? If the "final" diagnosis is set in hospitals why are there differences in registered cases between hospital registers and primary care records?
AMI diagnoses are made in the hospital and the general practitioners are informed about these. Primary care has a higher prevalence of AMI than hospital care and disease registers because it could include historical diagnoses (Herrett et al., 2013b). This statement is now included in the Introduction section in the manuscript.
2. Survival following AMI is dependent upon type of AMI where STEMIs in general have higher mortality then non-STEMIS. It is not clear how this is handled in the study. Does the data include information of type of AMI at all?
Please see our response to question 2 of reviewer 1.

3. The lower uptake of PCI/CABG among women can be related to more non-STEMIs among females.
Please see our response to a similar question of reviewer 3.

4. If type of AMI is unknown it is hard to see how type of treatment can be evaluated since treatment will depend on type of AMI. Matching will probably not solve the problem.
The treatments selected in this study were based on clinical guideline 172 'myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease' published by the National Institute of Health and Care Excellence, a UK national body providing guidelines on health and social care. Regarding matching, please see our response to a similar question of reviewer 3.
5. The dependent variable is time to death. We need the exact definition. Is time from death calculated from onset of the AMI, from treatment in primary care (index day) or from a possible discharge date from a hospital or a GP setting.
We thank the reviewer for the comment. For baseline characteristics, the medical records are reviewed on the 1st of January of the year the patient turned a specific age (60, 65, 70, or 75). The patients are then followed up with respect to death dates. The dependent variable is time from the start of the study (thus the 1st of January of the year the patient turned a specific age) to the death date, measured in days. We clarified this definition in the Methods section:
- Subsection 'Study design': Four cohorts of patients who were born between 1920 and 1940 and turned the initial age in 1987-2011 were selected.
- Subsection 'Variable selection': The baseline characteristics of patients were assessed on the 1st of January of the year they turned the cohort's age.
- Subsection 'Statistical analysis': A Cox's proportional hazard regression model was fitted to estimate the effect of a history of AMI and respective treatments on the hazard of all-cause mortality at different

ages. The outcome variable was time to death in days, i.e. from the 1st of January of the year the patient turned the cohort's age to the death date.

6. The final model includes several covariates including medication use. Are use of medication only registered after the treatment episode or are (some) of the medication in use also before the onset of the disease and start of the treatment? If data on some of the covariates are registered before the onset of the AMI they probably will work more like risk adjusters than treatment. This needs clarification.
We thank the reviewer for the comment. The description box of Table 2 explained that the prevalence of treatment is any treatment by the initial age, i.e. treatment could have started any time prior to the cohort's age and thus be prior or after the onset of a disease. We agree with the reviewer that treatment might alter risk factors. We believe that the alteration would be minimal as we used diagnosis of medical conditions instead of blood values. Therefore misclassification of health status due to time of recording of health indicators would be unlikely.

7. On the end of page 4 the term "ward" turns up. What is this and how does a ward relate to the general practice? A short introduction to the institutional setting is needed, including a description of typical pathway for AMI patients.
We thank the reviewer for the comment. 'Ward' in this context means postcode area or district. We substituted the word 'ward' with 'district' in the manuscript to avoid future confusion.

We are grateful for the work the editor and reviewers have conducted to improve our manuscript. We hope that we hereby addressed all the concerns raised by the reviewers and that our paper could be published in your journal.

We are looking forward to your reply.

Yours sincerely,
Lisanne Gitsels

Machine Learning and Statistics Laboratory
School of Computing Sciences
University of East Anglia
Norwich Research Park
Norwich NR4 7TJ
United Kingdom

References

Abildstrom S, Rasmussen S, Madsen M. Changes in hospitalization rate and mortality after acute myocardial infarction in Denmark after diagnostic criteria and methods changed. Eur Heart J 2005;26:990-5.

Chang WC, Kaul P, Westerhout CM, Graham MM, Fu Y, Chowdhury T, Armstrong PW. Impact of sex on long-term mortality from acute myocardial infarction vs unstable angina. Arch Intern Med. 2003;163(20):2476-2484. doi:10.1001/archinte.163.20.2476.

Chieffo A, Buchanan GL, Mauri F, Mehilli J, Vaquerizo B, Moynagh A, Mehran R, Morice MC. ACS and STEMI treatment: gender-related issues. EuroIntervention. 2012;8:P27e35. doi:10.4244/EIJV8SPA6.

Coronary Drug Project Research Group. Aspirin in coronary heart disease. Circulation. 1980; 62(6 Pt 2):V59-V62.

Greenland S, Morgenstern H. Matching and efficiency in cohort studies. American Journal of Epidemiology 1990;131(1):151-9.

Hardoon SL, Whincup PH, Petersen I, Capewell S, Morris RW. Trends in longer-term survival following an acute myocardial infarction and prescribing of evidenced-based medications in primary care in the UK from 1991: a longitudinal population-based study. Journal of Epidemiology and Community Health 2011;65(9):770-774. doi:10.1136/jech.2009.098087.

Hennekens, C, Buring, J, and Mayrent, S. Epidemiology in medicine. 1987. Boston: Little Brown and Company.

Herrett E, George J, Denaxas S, Bhaskaran K, Timmis A, Hemingway H, Smeeth L. Type and timing of heralding in ST-elevation and non-ST-elevation myocardial infarction: an analysis of prospectively collected electronic healthcare records linked to the national registry of acute coronary syndromes. European Heart Journal: Acute Cardiovascular Care 2013a; 2(3):235-45. doi:10.1177/2048872613487495.

Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, Timmis A, Hemingway H. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ 2013b;346:f2350. doi:10.1136/bmj.f2350.

National Institute for Health and Care Excellence. NICE clinical guideline 172. Myocardial infarction: cardiac rehabilitation and prevention of further MI. 2013a

National Institute for Health and Care Excellence. NICE clinical guideline 48. MI- secondary prevention: secondary prevention in primary and secondary care for patients following a myocardial infarction. 2013b

Reeves D, Springate DA, Ashcroft DM, Ryan R, Doran T, Morris R, Olier I, Kontopantelis E. Can analyses of electronic patient records be independently and externally validated? The effect of statins on the mortality of patients with ischaemic heart disease: a cohort study with nested case–control analysis. BMJ Open 2014;4:e004952. doi:10.1136/bmjopen-2014-004952.

Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. Circulation 2010;121:863-9.

Salomaa V, Ketonen M, Koukkunen H, Immonen-Raiha P, Lehtonen A, Torppa J, et al. The effect of correcting for troponins on trends in coronary heart disease events in Finland during 1993-2002: the FINAMI study. Eur Heart J 2006;27:2394-9.

Sanfilippo FM, Hobbs MST, Knuiman MW, Hung J. Impact of new biomarkers of myocardial damage on trends in myocardial infarction hospital admission rates from population-based administrative data. Am J Epidemiol 2008;168:225-33.

Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. BMJ

2012a;344:d8059. doi:10.1136/bmj.d8059.

Smolina K, Wright FL, Rayner M, Goldacre MJ. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circ Cardiovasc Qual Outcomes 2012b;5(4):532-540. doi:10.1161/CIRCOUTCOMES.111.964700.
New tables

Table 1 Prevalence coronary revascularisation given ischaemic heart disease (IHD)
Coronary
revascularisation n (%)
Age 60 CABG 751 (16%)
PCI 167 (3%)
Total* 881 (18%)

Age 65 CABG 2,479 (19%)
PCI 750 (6%)
Total* 3,069 (23%)

Age 70 CABG 4,606 (19%)
PCI 1,869 (8%)
Total* 6,113 (26%)

Age 75 CABG 5,036 (19%)
PCI 1,958 (7%)
Total* 6,601 (25%)
CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. *Some IHD patients had both CABG and PCI. The prevalence of coronary revascularisation by the initial ages was affected by calendar year (Figure A1 in the Online Data Supplements).

Table 2 Prevalence antiplatelet therapy in age cohorts
Cohort* DAPT** Aspirin only Other antiplatelet agent only
Age 60 122 (1%) 2,213 (13%) 119 (1%)
Age 65 1,079 (3%) 10,152 (23%) 387 (1%)
Age 70 4,097 (6%) 22,639 (31%) 802 (1%)
Age 75 5,565 (7%) 28,451 (37%) 1,009 (1%)
*The age cohorts included cases with history of acute myocardial infarction who were matched to three controls on sex, year of birth category, and general practice. **DAPT=dual antiplatelet therapy (aspirin plus second antiplatelet agent). The prevalence of treatment by the initial ages was affected by calendar year (Figure A1 in the Online Data Supplements).

Table 3 Adjusted effects of a history of ischaemic heart disease (IHD) on the hazard of all-cause mortality in 2001-2011
Cohort IHD* HR (95%CI)**
Age 65 No
Angina 1.25 (1.05-1.50)
Single AMI 1.68 (1.44-1.97)
Multiple AMI 2.02 (1.65-2.46)
Age 70 No
Angina 1.15 (1.03-1.28)
Single AMI 1.61 (1.46-1.78)
Multiple AMI 1.82 (1.60-2.06)

Age 75 No
Angina 1.24 (1.15-1.34)
Single AMI 1.57 (1.45-1.69)
Multiple AMI 1.80 (1.63-1.98)

*The age cohorts included cases with history of acute myocardial infarction (AMI) who were matched to three controls on sex, year of birth category, and general practice, where both cases and controls turned the cohort's age in 2001-2011. The hazard of mortality associated with single/multiple AMIs includes possible history of angina. **Adjusted for sex, year of birth, socioeconomic status, heart failure, other cardiovascular conditions, chronic kidney disease (only at ages 70 and 75), diabetes, hypertension, hypercholesterolaemia, coronary revascularisation, statin, beta blocker, ACE-inhibitor, calcium-channel blocker, aspirin, alcohol consumption, body mass index, smoking status, and general practice.

VERSION 2 – REVIEW

REVIEWER	Etienne Puymirat Hôpital Européen Georges Pompidou, Département de Cardiologie, Paris, France
REVIEW RETURNED	14-Nov-2016

GENERAL COMMENTS	Answers are correct and well detailed. Very interesting manuscript

REVIEWER	Terje P. Hagen Department of Health Management and Health Economics, University of Oslo, Norway
REVIEW RETURNED	18-Nov-2016

GENERAL COMMENTS	Most of my initial comments are handled in a proper way. I do however have a few additional remarks that need to be handled in the manuscript. Survival following AMI is dependent upon type of AMI where STEMIs in general have higher mortality then non-STEMIS. The authors inform the reviewers in their letter to the editor that data on STEMI/non-STEMI are not available. This also needs to be stated in the article. In the current version there is a general statement on lack of clinical information. However, the STEMI/non-STEMI distinction is crucial and needs an explicit discussion. The lower uptake of PCI/CABG among women can be related to more non-STEMIs among females. This does also need to be explicitly discussed.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Answers are correct and well detailed.
Very interesting manuscript

Reviewer: 4
Most of my initial comments are handled in a proper way. I do however have a few additional remarks

that need to be handled in the manuscript.

1. Survival following AMI is dependent upon type of AMI where STEMIs in general have higher mortality then non-STEMIS. The authors inform the reviewers in their letter to the editor that data on STEMI/non-STEMI are not available. This also needs to be stated in the article. In the current version there is a general statement on lack of clinical information. However, the STEMI/non-STEMI distinction is crucial and needs an explicit discussion.

In the Subsection 'Variable selection', it is explicitly stated that information on the type of AMI was not available. We added to the Subsection 'Study's strengths and limitations' the limitation that the data on type of AMI were not available in THIN, therefore this study could not distinguish between STEMI and non-STEMI and thus could not provide specific survival prospects for them.

2. The lower uptake of PCI/CABG among women can be related to more non-STEMIs among females. This does also need to be explicitly discussed.

A paper by Herrett et al. (2013) with data from the UK from 2003-2008 showed that coronary revascularisation was more prevalent in non-STEMIs than in STEMIs. As non-STEMIs are more common among women than among men (Herrett et al., 2013), it seems that type of AMI could not explain the sex difference in uptake of surgery present in our study with data from the UK from 1987-2011. In 2012, the European Society for Cardiology reviewed the sex difference in treatment after AMI, taking into account sex differences in risk profiles, and concluded that sex differences exist (Chieffo et al., 2012). We added this argument to the Discussion Section.

We are grateful for the work the editor and reviewers have conducted to improve our manuscript. We hope that we hereby addressed all the concerns raised by the reviewers and that our paper could be published in your journal.

We are looking forward to your reply.

References

Chieffo A, Buchanan GL, Mauri F, Mehilli J, Vaquerizo B, Moynagh A, Mehran R, Morice MC. ACS and STEMI treatment: gender-related issues. EuroIntervention. 2012;8:P27e35. doi:10.4244/EIJV8SPA6.

Herrett E, George J, Denaxas S, Bhaskaran K, Timmis A, Hemingway H, Smeeth L. Type and timing of heralding in ST-elevation and non-ST-elevation myocardial infarction: an analysis of prospectively collected electronic healthcare records linked to the national registry of acute coronary syndromes. European Heart Journal: Acute Cardiovascular Care 2013a; 2(3):235-45. doi:10.1177/2048872613487495.