Published in final edited form as:
Heart. 2013 June ; 99(11): 767–773. doi:10.1136/heartjnl-2012-303244.

Medication, reperfusion therapy and survival in a community-based setting of hospitalised myocardial infarction

Emily C O'Brien[1], **Kathryn M Rose**[1,2], **Chirayath M Suchindran**[3], **Til Stürmer**[1], **Patricia P Chang**[4], **Lloyd Chambless**[3], **Cameron S Guild**[5], and **Wayne D Rosamond**[1]

[1]Department of Epidemiology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA

[2]Health Sciences Research, SRA International, Inc., Durham, North Carolina, USA

[3]Department of Biostatistics, Gillings School of Global Public Health, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA

[4]Department of Cardiology, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA

[5]Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA

Abstract

Objective—To examine the survival benefit of multiple medical therapies in a large, community-based population of validated myocardial infarction (MI) events.

Design—Retrospective observational cohort study.

Setting—Population-based sample of 30 986 definite or probable MIs in residents of four US communities aged 35–74 years randomly sampled between 1987 and 2008 as part of the Atherosclerosis Risk in Communities Surveillance Study.

Interventions—None.

Main outcome measures—All-cause mortality 30, 90 and 365 days after discharge.

Results—We used unadjusted and propensity score (PS) adjusted models to examine the relationship between medical therapy use and mortality. In unadjusted models, each medication and procedure was inversely associated with 30-day mortality. After PS adjustment, the crude survival benefits were attenuated for all therapies except for intravenous tissue plasminogen

Correspondence to: Dr Emily O'Brien, Duke Clinical Research Institute, 2400 Pratt Street, Room 0311 Terrace Level, Durham, NC 27705, USA; emily.obrien@duke.edu.

Contributors EO designed the statistical analysis plan, analysed the data, and drafted and revised the paper. She is the guarantor. KR, CS and TS revised the statistical analysis plan and revised the paper. PC drafted and revised the paper. LC revised the statistical analysis plan. CG revised the paper. WR designed the surveillance component of the ARIC study, trained investigators, monitored data collection, revised the statistical analysis plan and drafted and revised the paper.

Competing interests None.

Ethics approval UNC Public Health Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing Additional unpublished data are available from the first author and can be included to the paper on editor or reviewer demand.

activator therapy (IV-tPA) and stent use. After inclusion of other therapies received during the event in regression models, risk ratio effect estimates (RR; (95% CI)) were attenuated for aspirin (0.66; (0.58 to 0.76) to 0.91 (0.80 to 1.03)), non-aspirin antiplatelets (0.74; (0.59 to 0.92) to 0.92 (0.72 to 1.18)), IV-tPA (0.50; (0.41 to 0.62) to 0.65 (0.52 to 0.80)) and stents (0.53 (0.40 to 0.69) to 0.68 (0.49 to 0.94)). Effect estimates remained stable for all other therapies and were similar for 90- and 365-day mortality endpoints.

Conclusions—We observed inverse associations between receipt of six medications and procedures for MI and all-cause mortality at 30, 90 and 365 days after adjustment for PS. The mortality benefits observed in this population-based setting are consistent with those reported in clinical trials.

INTRODUCTION

Acute myocardial infarction (AMI) is the most common direct cause of mortality due to coronary heart disease (CHD), and approximately 16% of patients who experience an AMI will die within 1 year of hospitalisation.[1] Death rates attributable to CHD have declined since the 1960s,[2–4] with nearly half of the decrease in CHD mortality attributable to medical advancements.[5] There is a rich literature of data from clinical trials and observational studies reporting mortality benefits of medical therapy after myocardial infarction (MI). However, clinical trials are often conducted in highly-selected patient populations and may not represent what is observed in clinical practice.[6–8] Observational studies provide a valuable perspective into the therapeutic benefits of medications and procedures in community-based, hospitalised settings and are increasingly using propensity score (PS) adjustment methods to account for non-randomised study designs.[9] However, few studies using PS to adjust for confounding have examined modelling strategies to account for the use of multiple therapies during a single hospitalised event.

In this study, we examined the association among 30-, 90- and 365-day all-cause mortality and receipt of 11 medical therapies commonly used for treatment of hospitalised MI in a population-based sample of the Atherosclerosis Risk in Communities (ARIC) Study surveillance communities. We used four unique PS strategies to account for the non-randomised study design and the effect of multiple medical therapies on all-cause mortality after hospitalisation in a large, community-based population of validated MI events sampled over 22 years.

METHODS

The design of the community surveillance component of the ARIC study has been described.[10] Briefly, it is a continuous retrospective surveillance study of hospitalised CHD events with mortality follow-up designed to estimate trends in CHD incidence and mortality using standardised criteria and methods in four US communities: Forsyth County, North Carolina; Jackson, Mississippi; eight suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Eligible events included hospitalised fatal and non-fatal MI occurring from 1987 to 2008 in 35–74-year-old residents of these communities. Details of the sampling scheme for the community surveillance component in the ARIC study have been previously reported.[11] Trained abstractors investigate hospitalisations randomly sampled

from annual discharge lists obtained from each hospital serving the four ARIC communities. Events are sampled on age, gender, community of residence and International Classification of Diseases (ICD-9) discharge codes, including 402, 410–414, 427, 428 and 518.4. Hospital records for sampled cases are reviewed, and relevant clinical information is abstracted onto standardised forms. Data items collected include presenting symptoms; timing of symptom onset; history of MI, angina and other cardiovascular conditions; inhospital medications, diagnostics and medical procedures; laboratory values for a number of relevant cardiac biomarkers; and up to three sets of 12-lead ECG readings. Regular and ongoing inter-abstractor agreement is assessed by evaluating concordance between data elements from a sample of cases abstracted independently by two abstractors. Internal quality control procedures at the ECG reading Centre are used to ensure reproducibility.

MI diagnostics

A computerised algorithm using evidence from ECG, history of chest pain and cardiac biomarker levels (total creatine phosphokinase, creatine phosphokinase-myocardial band, lactate dehydrogenase, troponin I and troponin T) was used to assign an MI diagnosis to sampled hospitalised events (Definite MI, Probable MI, Suspected MI, no MI or Unclassifiable). This analysis was restricted to events with a Definite or Probable MI diagnosis. Any event with abnormal or equivocal biomarker levels was further classified as ST- or non-ST segment elevation myocardial infarction (STEMI or NSTEMI) using pain presentation and Minnesota-coded ECG data from the first, third or last ECG performed during hospitalisation. Multiple hospitalisations occurring within 28 days were combined and treated as one event.

Medical therapies

Medications and procedures were obtained from hospital pharmacy records and medical record review during the abstraction process. Our analysis included data on seven medication classes (ATC Codes): aspirin (A01AD05, B01AC06, N02BA01), β blockers (C07), calcium channel blockers (C08), ACE inhibitors (ACEI; C09A, C09B), lipid-lowering medications (C10), non-aspirin antiplatelet agents (B01AC) and heparin (B01AB); and four reperfusion/revascularisation procedures: coronary artery bypass grafting (CABG), thrombolytic therapy (intracoronary or intravenous streptokinase, urokinase, anistreplase, anisoylated plasminogen streptokinase activator complex, or intravenous tissue plasminogen activator (IV-tPA) reperfusion), coronary angioplasty (percutaneous coronary intervention; PCI), and PCI with a stent. Each medication or procedure was classified as any receipt during hospitalisation or at discharge (yes or no). Because several new therapies were introduced during the study period, risk estimates for the following therapies were estimated beginning with the first study year for which complete treatment information was collected for all sampled events: heparin (beginning in 1992), ACEI (1992), non-aspirin antiplatelets (1997), lipid-lowering medications (1999) and stent implantation (1999).

All-cause mortality

We analysed three outcomes of interest: 30-, 90- and 365-day all-cause mortality. Deaths were confirmed by medical record review, state death records or linkage with the National

Death Index. The 30-, 90- and 365-day classifications represent the intervals from hospital admission date until date of death.

Exclusion criteria

From 1987 to 2008, 32 137 definite or probable MIs in patients aged 35–74 years were sampled in the ARIC surveillance communities. We excluded patients whose race was not classified as black or white (n=658) and due to insufficient sample sizes, black patients in Minnesota or Washington County, Maryland (n=493). After these exclusions, the final sample size for analysis was 30 985 definite or probable MI events.

Propensity score

PS represents the probability that a given subject will receive a treatment of interest, based on that subject's distribution of a selected set of covariates used to calculate the score. Given a treatment Z (Z=1 if treated, 0 if untreated) and observed covariates X, the PS is given as e(X)=prob(Z=1|X), or the probability that a patient with given values for covariates X will be treated. The score is created by regressing receipt of each medical therapy in separate logistic regression models on a set of covariates. The probability of receipt of treatment for each subject, based on the covariates in the model, was retained and used as the PS for that subject.

Candidate variables for inclusion in the PS were selected based on literature reviews, clinical knowledge and directed acyclic graphs. We selected a standard set of clinical covariates that are important risk factors for all-cause mortality: age (<45, 45–<55. 55–<65, 65+), male gender, race-centre cross classification (Jackson blacks, Jackson whites, Forsyth blacks, Forsyth whites, Minnesota whites and Washington whites), smoking status (ever vs never), cardiogenic shock, congestive heart failure, cardiac arrest during hospitalisation, history of diabetes, STEMI diagnosis, study year (1987–1991, 1992–1996, 1997–2001, 2002–2008), prior angioplasty and prior CABG.

Statistical analyses

We created medical therapy-specific PS models of the association between the standard set of covariates and the receipt of each of 11 medical therapies. Because medications are rarely received in isolation, we created three sets of PS to account for the effect of other medications and procedures received during hospitalisation: (1) PS using the standard set of clinical covariates demonstrated to be associated with survival after hospitalisation, without consideration of receipt of other medications; (2) PS including all other medications and procedures in addition to this standard set of covariates; and (3) PS with the standard set of covariates and the dichotomised total number of other medical therapies received during hospitalisation (<3 and ≥3). After creation of the scores, the model-specific distributions of covariates within PS quintiles were compared, and model diagnostics were assessed. C-statistic values for all models ranged from 0.63 to 0.85. Distributions of clinical covariates were comparable between treated and untreated patients within score quintiles, as were mean PS (data not shown). We excluded all observations in the non-overlap regions of the PS distributions of the treated and untreated patients to ensure positivity and trimmed 5% of the observations at each tail to eliminate potential bias introduced by subjects who were

treated contrary to prediction.[12] PS was then included in regression models as a set of binary variables representing PS distribution quintiles.

All estimates presented are weighted to account for the ARIC surveillance sampling scheme.[10] We used a multivariable log-linear model with Poisson error distribution, which produces a risk ratio (RR) effect estimate, to estimate the associations between receipt of each medical therapy and 30-, 90- and 365-day all-cause mortality. To account for the complex sampling scheme, all analyses were conducted using SAS-callable SUDAAN (release V.9.2; Research Triangle Institute, Research Triangle Park, North Carolina, USA).

RESULTS

Table 1 shows selected characteristics for 30 986 MI patients, overall and by mortality strata (all-cause mortality within 30, 90 and 365 days of discharge). The unadjusted risk of death within 30 days of hospitalisation for definite or probable MI was 7.5%; within 90 days, 8.6%; and within 365 days, 10.0%. Compared with the entire population of hospitalised MI patients, those who died within 30 days of hospitalisation were older, less likely to be male subjects, and more likely to be black subjects, have a history of stroke, have diabetes, arrive by emergency medical services (EMS) and be classified as NSTEMI. Similar patterns were observed in patients who died within 90 days of hospitalisation and those who died within 365 days of hospitalisation. Patients who died within 30, 90 or 365 days of hospitalisation were less likely to have a prehospital delay time of less than 2 h. Of all deaths that occurred within 30 days of hospitalisation, a higher proportion were observed in earlier time periods (33.4% in 1987–1991) than in the later time periods (19.5% in 2002–2008). A similar pattern was observed for deaths within 90 days (34.3% in 1987–1991 vs 32.5% in 2002–2008) and for deaths within 365 days (32.0% in 1987–1991 vs 23.5% in 2002–2008).

Figure 1 shows the distribution of total medications prescribed per event by study year category. In this figure, events were grouped into intervals of 5, 6 or 7 years to promote stability in CI estimates. The mean total number of medications per hospitalisation increased from 1.77 (95% CI 1.73 to 1.81) in the first study year interval to 4.76 (95% CI 4.69 to 4.83) in the fourth interval. Over time, the normalised distribution of total number of medications per hospitalisation shifted to the right, indicating a higher number of medications per hospitalisation in recent years compared with earlier years.

Table 2 presents the total percentage of patients receiving each medical therapy of interest over the study period (%; 95% CI) and the unadjusted risk of mortality at 30, 90 and 365 days following hospitalisation in patients who received each medical therapy. Aspirin was the most commonly used medication throughout the study period, followed by β blockers, heparin and lipid-lowering medications. Angioplasty was the most commonly used procedure, with over half of angioplasty patients receiving a stent. Crude mortality risks were lower for patients receiving any of the medications or procedures of interest than in the overall population.

Table 3 presents risk ratios estimating the association between receipt of each medical therapy and 30-day all-cause mortality by PS regression strategy. The unadjusted estimates

(Model A. Unadjusted) indicate reductions in all-cause mortality associated with each medication and procedure. After inclusion of the PS in regression models (Model B. PS Only), the crude mortality effects were attenuated for all therapies except for IV-tPA and stent use. After inclusion of the PS in regression models (Model C. PS+all other medical therapies), effect estimates (RR; (95% CI)) were substantially attenuated for aspirin and moderately attenuated for non-aspirin antiplatelets, IV-tPA and stents. Model D shows results from a model including PS created from the standard set of covariates plus a variable representing dichotomised number of total medications per hospitalised event (<3, ≥3). Estimates from this model were similar to those from Model C, with the exception of stents (0.51 (0.42 to 0.63)) and IV-tPA (0.56 (0.41 to 0.75)), both of which showed increased mortality benefit in Model D compared with Model C. Effect estimates from this model were moderately attenuated for all medical therapies except for angioplasty and IV-tPA, which were comparable with the estimates obtained from Model D.

Because mortality benefits associated with pharmaceutical therapy may differ among patients undergoing reperfusion, we ran two sets of sensitivity analyses of medication use and 30-day mortality in IV-tPA and PCI patients, respectively. For patients receiving PCI, we found similar mortality benefits for all medications except for calcium channel blockers, which were no longer protective. For IV-tPA, we found larger mortality benefits associated with the use of aspirin, β blockers and non-aspirin antiplatelets; the protective effect of calcium-channel blockers also disappeared in this subgroup.

Tables 4 and 5 present the association between receipt of each medical therapy and 90- and 365-day mortality (respectively) using the same strategies used to model 30-day mortality. Similar patterns in mortality by model strategy were observed for both 90-and 365-day endpoints. To examine the stability of effect estimates over time, we ran a sensitivity analysis limiting our dataset to events occurring from 2002 to 2008. Estimates from this analysis were similar to those obtained from the entire set of events.

DISCUSSION

To our knowledge, this is the first study to examine how the mortality benefits of evidence-based therapies change when accounting for the use of multiple medications in a population-based sample of validated MI events. In this study, we observed inverse associations between medication use and all-cause mortality at 30, 90 and 365 days after hospitalised MI for β blockers, calcium channel blockers, aspirin, lipid-lowering medications, non-aspirin antiplatelets and ACEI after adjustment for PS created from a standard set of clinical covariates. These inverse associations were attenuated but remained significant after adding all medical therapies to the PS regression model, with the exception of non-aspirin antiplatelets, which were no longer protective after inclusion of all therapies. Similar patterns were observed when examining 90- and 365-day mortality endpoints. Our results are similar in magnitude and direction to those observed in a number of large-scale clinical trials for β blockers,[13, 14] aspirin,[15] calcium channel blockers,[16] ACEI,[17, 18] heparin[19] and lipid-lowering medications.[20] As has been observed in number of clinical trials, the mortality benefit of non-aspirin antiplatelets was attenuated substantially after accounting for the use of other medications.[21, 22]

Inverse associations between receipt of inhospital procedures and 30-day mortality were observed with the inclusion of PS from a standard set of clinical covariates and remained stable for all four procedure groups after inclusion of variables representing number and type of other medical therapies in regression models. Observed mortality benefits in this study are similar to those reported in clinical trials of PCI,[23, 24] PCI with stent,[23, 25] IV-tPA and CABG.[26]

The consistency of our study results with those of clinical trials further strengthens existing evidence for real-world efficacy of commonly used MI therapies. This study is unique in its analysis of all-cause mortality and medication receipt in a community-based, observational setting. Studies of causal inference of medication use and survival in cardiovascular disease are often structured as randomised clinical trials, widely considered the gold standard for causal inference in the study of treatment effects.[27] However, clinical trials have stringent inclusion and exclusion criteria, and evidence from several studies indicates that clinical trial populations may not represent how AMI patients are treated in routine clinical practice.[6–8] In the current study, we used rigorous methodology and careful covariate selection to minimise bias typically found in observational analyses.

Because clinical trials usually focus on the effect of a single therapy in isolation, the benefit of common cardiovascular therapies in the context of multiple medications is often unclear. To address the issue of whether therapeutic benefits persist in the setting of multiple medications, we created three sets of PS including the number and type of other medical therapies administered during hospitalisation. Results from these models suggest mortality benefits at 30, 90 and 365 days for β blockers, aspirin, lipid-lowering medications and ACEI even after accounting for the presence of other medications during creation of PS. Similar associations for all mortality endpoints were found when all variables used to create the PS were included in a standard loglinear regression model.

Strengths

The ARIC community surveillance study offers a number of advantages in the study of medical therapy for acute MI and all-cause mortality after discharge. The study population is a large, racially and geographically diverse community-based sample with validated MI diagnostics. As clinical data are collected from randomly sampled hospitalised events, selection bias is minimised relative to typical observational cohort studies, where the patients who elect not to participate are often sicker and poorer than the rest of the patient population. Because the ARIC study monitors hospitalised events over a 22-year period, we were able to observe associations between medical therapy and mortality over a period of changing clinical practice landscape. Additionally, because of the large number of validated events in this population, we had adequate statistical power to detect medical therapy benefits for shorter-term timepoints. Finally, the rich clinical data collected by the ARIC study, including presence of comorbidities, procedure history, inhospital complications and STEMI/NSTEMI classification, allowed us to account for the presence of potentially important confounders, an integral component to observational analyses of medication use and postdischarge mortality.

Limitations

Because the ARIC community surveillance study is observational in nature, assignment of patients to medical therapies of interest is not randomised. While we tried to account for major known confounders through the use of PS, unmeasured confounding may exist. Additionally, the retrospective nature of the study limited our ability to account for the potential confounding effect of variables not collected as part of the study protocol. For patients discharged on aspirin, we did not have information on dosage or whether aspirin was prescribed for pain therapy or antiplatelet therapy. Finally, we were unable to assess prescription filling patterns or modifications to medication regimens after discharge.

As the proportion of MI patients receiving multiple medications during hospitalisation continues to increase, so does the importance of accounting for the effect of all therapies when analysing the survival benefit of a particular medication or revascularisation procedure. Results from well-designed clinical trials and observational studies assessing mortality reductions associated with cardiovascular medications and procedures have contributed to substantial improvements in the quality of care for hospitalised AMI over the past decades. Future research should assess the benefit of emerging therapies from a comprehensive perspective of the course of inhospital treatment for acute MI.

Acknowledgments

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C and HHSN268201100012C). The authors thank the staff and participants of the ARIC study for their important contributions.

References

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2009; 119:480–6. [PubMed: 19171871]
2. Floyd KC, Yarzebski J, Spencer FA, et al. A 30-year perspective (1975–2005) into the changing landscape of patients hospitalized with initial acute myocardial infarction: Worcester Heart Attack Study. Circ Cardiovasc Qual Outcomes. 2009; 2:88–95. [PubMed: 20031820]
3. Fox CS, Evans JC, Larson MG, et al. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study. Circulation. 2004; 110:522–7. [PubMed: 15262842]
4. Gale CP, Cattle BA, Woolston A, et al. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003–2010. Eur Heart J. 2012; 33:630–9. [PubMed: 22009446]
5. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. N Engl J Med. 2007; 356:2388–98. [PubMed: 17554120]
6. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. JAMA. 1992; 268:1417–22. [PubMed: 1512909]
7. Steg PG, Lopez-Sendon J, Lopez de Sa E, et al. External validity of clinical trials in acute myocardial infarction. Arch Intern Med. 2007; 167:68–73. [PubMed: 17210880]
8. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet. 2005; 365:82–93. [PubMed: 15639683]
9. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med. 1997; 127(8 Pt 2):757–63. [PubMed: 9382394]

10. White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the atherosclerosis risk in communities (ARIC) study: Methods and initial two years' experience. J Clin Epidemiol. 1996; 49:223–33. [PubMed: 8606324]
11. Rosamond WD, Chambless LE, Sorlie PD, et al. Trends in the sensitivity, positive predictive value, false-positive rate, and comparability ratio of hospital discharge diagnosis codes for acute myocardial infarction in four US communities, 1987–2000. American Journal of Epidemiology. 2004; 160:1137–46. [PubMed: 15583364]
12. Westreich D, Cole SR. Invited commentary: positivity in practice. Am J Epidemiol. 2010; 171:674–7. discussion 678–681. [PubMed: 20139125]
13. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. Lancet. 1986; 2:57–66. [PubMed: 2873379]
14. The MIAMI Trial Research Group. Metoprolol in acute myocardial infarction. Patient population. Am J Cardiol. 1985; 56:10G–14G.
15. Antithrombotic Trialists' Collatoration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002; 324:71–86. [PubMed: 11786451]
16. Secondary prevention reinfarction Israeli nifedipine trial (SPRINT). A randomized intervention trial of nifedipine in patients with acute myocardial infarction. The Israeli Sprint Study Group. Eur Heart J. 1988; 9:354–64. [PubMed: 2898363]
17. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. Circulation. 1998; 97:2202–12. [PubMed: 9631869]
18. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet. 1995; 345:669–85. [PubMed: 7661937]
19. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet. 1992; 339:753–70. [PubMed: 1347801]
20. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996; 335:1001–9. [PubMed: 8801446]
21. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005; 366:1607–21. [PubMed: 16271642]
22. Chua D, Lo C, Babor EM. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction. N Engl J Med. 2005; 352:2647–8. author reply 2647–8. [PubMed: 15972875]
23. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med. 1999; 341:1949–56. [PubMed: 10607811]
24. Wilson SH, Bell MR, Rihal CS, et al. Infarct artery reocclusion after primary angioplasty, stent placement, and thrombolytic therapy for acute myocardial infarction. Am Heart J. 2001; 141:704–10. [PubMed: 11320356]
25. Maillard L, Hamon M, Khalife K, et al. A comparison of systematic stenting and conventional balloon angioplasty during primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. STENTIM-2 Investigators. J Am Coll Cardiol. 2000; 35:1729–36. [PubMed: 10841218]
26. Serruys PW, Ong AT, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol. 2005; 46:575–81. [PubMed: 16098418]

27. Feinstein AR. Current problems and future challenges in randomized clinical trials. Circulation. 1984; 70:767–74. [PubMed: 6488491]

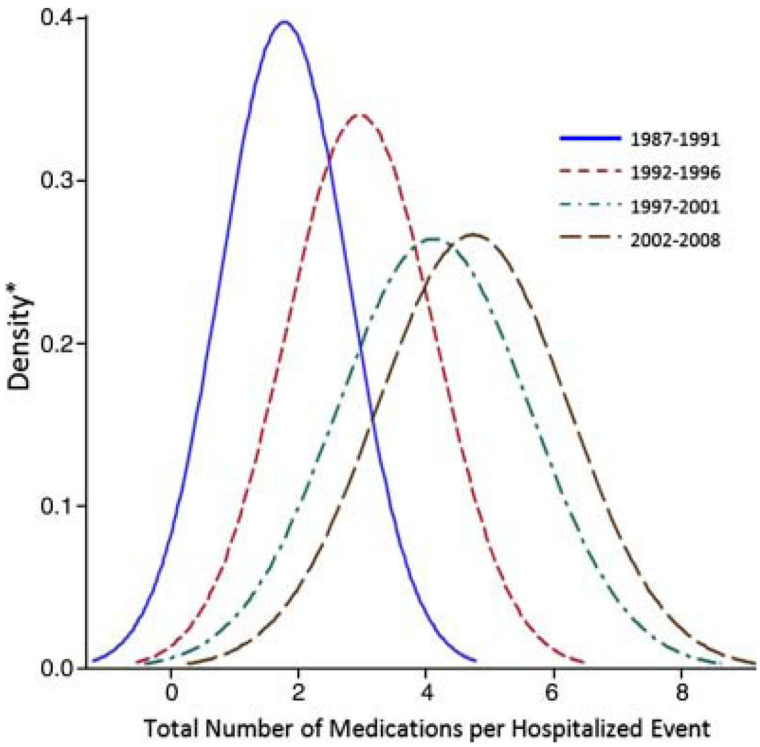

Figure 1.

Normalised density plot of total medications per hospitalisation for definite/probable myocardial infarction by study year category: the Atherosclerosis Risk in Communities Surveillance Study (1987–2008). *Density indicates the likelihood that the random variable(total number of medications per hospitalised event) will take on a given value from 0–8. Higher density reflects higher probability of observing the corresponding number of medications. This figure is only reproduced in colour in the online version.

Table 1

Baseline patient and event characteristics of definite and probable MI patients overall and by primary outcomes of interest in the ARIC Community Surveillance Study, 1987–2008

Variable	All patients N=30 986* % (SE)	Death within 30 days† N=2337 % (SE)	Death within 90 days N=2669 % (SE)	Death within 365 days N=3106 % (SE)
Age in years, mean (SD)	60.4 (0.09)	64.5 (0.28)	64.2 (0.29)	64.0 (0.28)
Male gender	65.7 (0.42)	58.4 (1.53)	58.1 (1.51)	58.8 (1.4)
Race-centre classification				
Forsyth black	12.3 (0.33)	13.0 (1.14)	13.6 (1.09)	16.9 (1.16)
Forsyth white	10.6 (0.30)	11.6 (1.14)	12.0 (1.14)	11.1 (1.03)
Jackson black	10.6 (0.28)	15.1 (1.14)	15.6 (1.12)	16.7 (1.10)
Jackson white	28.7 (0.42)	8.4 (1.45)	28.1 (1.43)	26.3 (1.30)
Minnesota whites	20.4 (0.36)	7.1 (1.19)	15.9 (1.12)	15.0 (1.03)
Washington whites	17.5 (0.30)	7.3 (0.93)	14.8 (0.87)	14.0 (0.81)
Comorbidities				
Prior MI	32.6 (0.44)	34.8 (1.47)	35.2 (1.42)	36.6 (1.38)
Hypertension	63.6 (0.44)	64.4 (1.53)	64.1 (1.52)	65.9 (1.42)
Diabetes	25.0 (0.42)	26.8 (1.28)	26.2 (1.22)	28.0 (1.22)
Stroke	9.3 (0.28)	17.2 (1.23)	17.7 (1.15)	17.4 (1.1)
Length of stay in days, mean (SD)	7.9 (0.09)	7.9 (0.26)	10.1 (0.37)	10.3 (0.37)
EMS transport	42.1 (0.47)	52.5 (1.59)	52.9 (1.55)	52.2 (1.47)
Prehospital delay‡				
<2 h	27.4 (0.40)	20.6 (1.26)	20.0 (1.18)	19.5 (1.08)
Unknown	11.7 (0.39)	27.0 (0.60)	27.4 (1.75)	25.7 (1.61)
Event classification§				
STEMI	19.7 (0.32)	21.0 (1.13)	20.1 (1.05)	18.8 (0.96)
NSTEMI	65.5 (0.44)	69.8 (1.42)	69.5 (1.40)	69.7 (1.34)
Study year				
1987–1991	24.3 (0.36)	33.4 (1.47)	34.2 (1.45)	32.0 (1.35)
1992–1996	25.0 (0.38)	25.0 (1.37)	23.9 (1.30)	23.2 (1.24)
1997–2001	23.8 (0.36)	22.2 (1.24)	21.4 (1.16)	21.3 (1.10)
2002–2008	27.0 (0.42)	19.5 (1.26)	20.5 (1.29)	23.5 (1.29)
Receipt of reperfusion¶	46.2 (0.45)	20.7 (1.03)	20.3 (1.00)	20.0 (0.95)
Total number of medications received				
0	4.5 (0.25)	3.1 (0.23)	3.0 (0.23)	3.0 (0.23)
1	9.8 (0.31)	8.9 (0.32)	8.7 (0.32)	8.5 (0.32)
2	17.0 (0.36)	17.0 (0.37)	16.9 (0.38)	16.9 (0.38)
3	21.2 (0.36)	21.6 (0.38)	21.7 (0.38)	21.8 (0.38)
4+	47.5 (0.44)	49.5 (0.46)	49.7 (0.46)	49.8 (0.47)

*Weighted number of definite or probable MI events.

†All-cause mortality from the first day of the hospitalised event.

[‡] Prehospital delay was defined as the interval from the earliest symptom onset time to hospital arrival time.

[§] STEMI defined as ST-elevation at any site on either the first or last ECG.

[¶] Reperfusion included thrombolysis, PCI with or without stent, and CABG.

ARIC, Atherosclerosis Risk in Communities; CABG, coronary artery bypass grafting; MI, myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction.

Table 2

Unadjusted risk of 30, 90 and 365-day mortality* and receipt of medications and procedures†: the ARIC Community Surveillance Study, 1987–2008

			All-cause mortality risk (%)					
	% Receiving (95% CI)		30-day (95% CI)		90-day (95% CI)		365-Day (95% CI)	
Medications‡								
Aspirin	82.4	81.6 to 83.2	4.6	4.3 to 4.9	5.4	5.0 to 5.7	6.5	6.1 to 6.9
BB	68.0	67.1 to 68.9	4.3	3.9 to 4.7	5.1	4.7 to 5.6	6.2	5.7 to 6.7
CCB	44.0	43.1 to 44.9	6.3	5.8 to 6.9	7.6	7.0 to 8.3	8.8	8.1 to 9.6
ACEI	53.9	52.8 to 55.0	4.7	4.2 to 5.3	5.6	5.0 to 6.3	7.3	6.6 to 8.1
Heparin	68.0	66.9 to 69.1	5.4	5.0 to 5.9	6.2	5.7 to 6.8	7.5	7.0 to 8.1
Lipid-lowering medication	67.3	65.8 to 68.8	2.7	2.3 to 3.1	3.0	2.9 to 4.0	4.9	4.3 to 5.7
Non-AAP	54.5	53.1 to 55.9	3.2	2.8 to 3.6	3.7	3.3 to 4.2	4.9	4.4 to 5.5
Procedures								
CABG	14.3	13.7 to 14.9	3.9	3.3 to 4.5	4.7	4.0 to 5.5	5.2	4.5 to 6.1
All PCI	28.0	27.3 to 28.7	2.6	2.2 to 2.9	2.8	2.4 to 3.2	3.3	2.9 to 3.8
IV-tPA	11.7	11.3 to 12.1	4.6	3.9 to 5.4	5.0	4.2 to 5.8	5.5	4.7 to 6.5
PCI with stent	31.3	30.1 to 32.5	2.1	1.7 to 2.7	2.4	1.9 to 3.0	3.2	2.6 to 3.8

*All-cause mortality within 30, 90 or 365 days of hospital arrival date.

†Medication or procedure use at any point during hospitalisation or medication prescription at discharge.

‡Percentage denominators limited to study years where specific medication information was collected.

ACEI, ACE inhibitors; ARIC, Atherosclerosis Risk in Communities; BB, β blockers; CABG, coronary artery bypass graft; CCB, calcium-channel blockers; IV-tPA, intravenous tissue plasminogen activator Non-AAP, non-aspirin antiplatelets; PCI, percutaneous coronary intervention.

Table 3

Risk ratios for medical therapy use* and 30-day mortality† among hospitalised MI patients by propensity score (PS) analytic strategy: the ARIC community surveillance study (1987–2008)

	Model A. Unadjusted		Model B. PS: standard covariates only‡		Model C. PS: standard covariates +all other medical therapies§		Model D. PS: standard covariates +number of other therapies (categorical¶)	
Therapy	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Medication								
Aspirin	0.21	0.19 to 0.24	0.66	0.58 to 0.76	0.68	0.59 to 0.78	0.65	0.57 to 0.75
β Blockers	0.30	0.26 to 0.34	0.67	0.58 to 0.76	0.71	0.62 to 0.81	0.78	0.68 to 0.89
Calcium channel blockers	0.74	0.66 to 0.84	0.80	0.70 to 0.92	0.85	0.74 to 0.98	0.77	0.66 to 0.90
ACE inhibitors	0.53	0.45 to 0.61	0.66	0.56 to 0.78	0.70	0.59 to 0.82	0.71	0.60 to 0.84
Heparin	0.59	0.51 to 0.67	0.86	0.73 to 1.01	0.92	0.79 to 1.07	0.96	0.81 to 1.14
Lipid-lowering medications	0.22	0.17 to 0.27	0.51	0.40 to 0.65	0.57	0.44 to 0.73	0.71	0.53 to 0.96
Non-aspirin antiplatelets	0.32	0.27 to 0.39	0.74	0.59 to 0.92	0.92	0.72 to 1.18	0.91	0.70 to 1.18
Procedure								
CABG	0.47	0.40 to 0.56	0.60	0.50 to 0.72	0.53	0.43 to 0.66	0.64	0.53 to 0.76
All PCI	0.27	0.23 to 0.31	0.45	0.38 to 0.54	0.48	0.39 to 0.59	0.51	0.43 to 0.61
IV-tPA	0.58	0.48 to 0.69	0.50	0.41 to 0.62	0.65	0.52 to 0.80	0.51	0.42 to 0.63
PCI with stent	0.88	0.69 to 1.13	0.53	0.40 to 0.69	0.68	0.49 to 0.94	0.56	0.41 to 0.75

*Medication or procedure use at any point during hospitalisation or medication prescription at discharge.

†All-cause mortality within 30 days of the hospital arrival date.

‡Standard covariates included age, gender, race, smoking status, CHF, diabetes, prior MI, cardiac arrest, cardiogenic shock, prior cardiac procedures, STEMI classification, study year and study centre.

§Quintiles of PS values calculated separately for treated and untreated patients after eliminating non-overlapping scores and trimming.

¶Categories of medication number were <3 and 3+.

ARIC, Atherosclerosis Risk in Communities; CABG, coronary artery bypass grafting; IV-tPA, intravenous tissue plasminogen activator; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, relative risk; STEMI, ST segment elevation myocardial infarction.

Table 4

Risk ratios for medical therapy use* and 90-day mortality† among hospitalised MI patients by propensity score (PS) analytic strategy: the ARIC community surveillance study (1987–2008)

	Model A. Unadjusted		Model B. PS: standard covariates only‡		Model C. PS: standard covariates +all other medical therapies§		Model D. PS: standard covariates +number of other therapies (categorical¶)	
Therapy	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Medication								
Aspirin	0.23	0.20 to 0.25	0.68	0.60 to 0.77	0.71	0.63 to 0.81	0.68	0.60 to 0.77
β Blockers	0.32	0.28 to 0.36	0.70	0.62 to 0.80	0.75	0.66 to 0.85	0.80	0.71 to 0.91
Calcium channel blockers	0.81	0.72 to 0.91	0.86	0.75 to 0.99	0.92	0.80 to 1.05	0.83	0.72 to 0.97
ACE inhibitors	0.58	0.50 to 0.67	0.69	0.59 to 0.81	0.73	0.63 to 0.86	0.74	0.63 to 0.87
Heparin	0.61	0.53 to 0.71	0.89	0.76 to 1.03	0.94	0.81 to 1.10	0.97	0.83 to 1.14
Lipid-lowering medications	0.25	0.20 to 0.31	0.57	0.44 to 0.73	0.63	0.48 to 0.82	0.73	0.55 to 0.98
Non-aspirin antiplatelets	0.34	0.28 to 0.40	0.74	0.60 to 0.92	0.90	0.71 to 1.14	0.87	0.67 to 1.14
Procedure								
CABG	0.50	0.42 to 0.60	0.64	0.54 to 0.77	0.59	0.48 to 0.74	0.67	0.56 to 0.81
All PCI	0.26	0.22 to 0.30	0.44	0.37 to 0.52	0.46	0.38 to 0.56	0.49	0.41 to 0.58
IV-tPA	0.55	0.46 to 0.65	0.50	0.41 to 0.60	0.65	0.53 to 0.79	0.52	0.42 to 0.63
PCI with stent	0.26	0.21 to 0.34	0.50	0.38 to 0.65	0.60	0.44 to 0.83	0.51	0.39 to 0.68

*Medication or procedure use at any point during hospitalisation or medication prescription at discharge.

†All-cause mortality within 90 days of the hospital arrival date.

‡Standard covariates included age, gender, race, smoking status, CHF, diabetes, prior MI, cardiac arrest, cardiogenic shock, prior cardiac procedures, STEMI classification, study year and study centre.

§Quintiles of PS values calculated separately for treated and untreated patients after eliminating non-overlapping scores and trimming.

¶Categories of medication number were <3 and 3+.

ARIC, Atherosclerosis Risk in Communities; CABG, coronary artery bypass grafting; IV-tPA, intravenous tissue plasminogen activator; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, relative risk; STEMI, ST segment elevation myocardial infarction.

Table 5

Risk ratios for medical therapy use[*] and 365-day mortality[†] among hospitalised MI patients by propensity score (PS) analytic strategy: the ARIC community surveillance study (1987–2008)

	Model A. Unadjusted		Model B. PS: standard covariates only[‡]		Model C. PS: standard covariates +all other medical therapies[§]		Model D. PS: standard covariates +number of other therapies (categorical[¶])	
Therapy	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Medication								
Aspirin	0.24	0.22 to 0.27	0.65	0.58 to 0.74	0.70	0.62 to 0.79	0.67	0.59 to 0.76
β Blockers	0.34	0.30 to 0.38	0.69	0.61 to 0.77	0.73	0.64 to 0.82	0.79	0.69 to 0.89
Calcium channel blockers	0.80	0.72 to 0.90	0.86	0.76 to 0.98	0.91	0.80 to 1.03	0.84	0.73 to 0.96
ACE inhibitors	0.66	0.58 to 0.76	0.73	0.62 to 0.85	0.76	0.65 to 0.88	0.77	0.66 to 0.89
Heparin	0.61	0.54 to 0.70	0.89	0.77 to 1.02	0.94	0.82 to 1.09	0.99	0.85 to 1.15
Lipid-lowering medications	0.31	0.25 to 0.37	0.61	0.49 to 0.76	0.69	0.54 to 0.87	0.76	0.58 to 1.00
Non-aspirin antiplatelets	0.37	0.31 to 0.43	0.76	0.62 to 0.93	0.94	0.76 to 1.17	0.92	0.72 to 1.17
Procedure								
CABG	0.48	0.41 to 0.57	0.62	0.52 to 0.74	0.59	0.48 to 0.72	0.65	0.55 to 0.77
All PCI	0.26	0.23 to 0.30	0.45	0.39 to 0.53	0.49	0.41 to 0.59	0.50	0.43 to 0.59
IV-tPA	0.52	0.44 to 0.62	0.49	0.41 to 0.60	0.63	0.52 to 0.77	0.51	0.42 to 0.62
PCI with stent	0.28	0.23 to 0.35	0.51	0.41 to 0.65	0.63	0.48 0.83	0.56	0.44 to 0.71

[*] Medication or procedure use at any point during hospitalisation or medication prescription at discharge.

[†] All-cause mortality within 365 days of the hospital arrival date.

[‡] Standard covariates included age, gender, race, smoking status, CHF, diabetes, prior MI, cardiac arrest, cardiogenic shock, prior cardiac procedures, STEMI classification, study year and study centre.

[§] Quintiles of PS values calculated separately for treated and untreated patients after eliminating non-overlapping scores and trimming.

[¶] Categories of medication number were <3 and 3+.

ARIC, Atherosclerosis Risk in Communities; CABG, coronary artery bypass grafting; IV-tPA, intravenous tissue plasminogen activator; MI, myocardial infarction; PCI, percutaneous coronary intervention; RR, relative risk; STEMI, ST segment elevation myocardial infarction.