COMMUNITY PATTERNS OF ACUTE MYOCARDIAL INFARCTION THERAPY AND SURVIVAL

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ABSTRACT

EMILY O'BRIEN: Community Patterns of Acute Myocardial Infarction Therapy and Survival
(Under the direction of Wayne Rosamond)

Background. Reports from clinical trials and observational studies have characterized recent temporal trends and treatment patterns for AMI. However, have examined differences in patterns of treatment for patients presenting with ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI). Additionally, reports on survival after AMI using propensity scores accounting for all medical therapies received during hospitalization are limited. We examined 21-year trends in the use of 10 medical therapies and procedures by STEMI and NSTEMI classification and associated survival using propensity score (PS) adjustment in the ARIC Community Surveillance Study (ARIC).

Methods. We analyzed data from 30986 definite or probable MIs between 1987 and 2008 among all residents 35-74 years of age in the four geographically defined US communities of the ARIC Study. We used weighted multivariable Poisson regression to estimate average annual percent changes in medical therapy use over the study period. We then used 4 PS adjustment strategies to account for the non-randomized study design and the receipt of other medical therapies during hospitalization.

Results. From 1987 – 2008, 6106 (19.7%) hospitalized events were classified as STEMI, and 20302 (65.5%) were classified as NSTEMI. Among STEMI patients, increases (%; 95% CI) were noted in the use of ACE inhibitors (6.4; 5.7, 7.2), non-aspirin anti-platelets (5.0; 4.0, 6.0), lipid-lowering medications (4.5; 3.1, 5.8), beta blockers (2.7; 2.4, 3.0), aspirin (1.2; 1.0, 1.3), and heparin (0.8; 0.4, 1.3). Among NSTEMI patients, the

use of ACE inhibitors (5.5; 5.0, 6.1), non-aspirin anti-platelets (3.7; 2.7, 4.7), lipid-lowering medications (3.0; 1.9, 4.1), beta blockers (4.2; 3.9, 4.4) increased. Calcium channel blocker use decreased for both STEMI (-8.8%;-9.6,-8.0) and NSTEMI (-5.6; -6.1,-5.1) patients over the study period. Medication and procedure use was associated with decreased risk of mortality at 30, 90, and 365 days after hospitalization for beta blockers, lipid lowering medications, aspirin, PCI, CABG and t-PA, even after adjustment for all medications received during hospitalization.

Conclusion. We found trends of increasing use of evidence-based medicine for both STEMI and NSTEMI patients over the past 22 years. Future research should examine the broader public health impact of increasing adherence to clinical therapy guidelines.

ACKNOWLEDGMENTS

To the casual observer, a doctoral dissertation may appear to be solitary work. However, to complete a project of this magnitude requires a network of support, and for this I am indebted to many people. I am most especially grateful to my advisor, Dr. Wayne Rosamond; my parents, Carol and Jeremy; and my siblings, Peter, Colin, and Jenny, for their prayers, guidance and support.

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LIST OF ABBREVIATIONS

MI = Myocardial Infarction

STEMI = ST Elevation Myocardial Infarction

NSTEMI = Non-ST Elevation Myocardial Infarction

CHD = Coronary Heart Disease

AHA = American Heart Association

PCI = Percutaneous Coronary Intervention

NRMI = National Registry of Myocardial Infarction

RCT = Randomized Controlled Trial

CABG = Coronary Artery Bypass Grafting

IV = Intravenous

T-PA = Tissue Plasminogen Activator

ACEI = ACE Inhibitors

BB = Beta Blockers

CCB = Calcium Channel Blockers

ARIC = Atherosclerosis Risk in Communities Study

PS = Propensity Score

EMS = Emergency Medical System

PREDICT = Predicting Risk of Death in Cardiac Disease Tool

I. INTRODUCTION

Coronary heart disease (CHD) is a major public health burden and the largest killer of American males and females. In 2005, CHD was responsible for 1 of every 5 deaths in the United States.[9] Acute myocardial infarction (MI) is the most common direct cause of mortality due to CHD. Each year, there are 610,000 new MIs and 325,000 recurrent MIs.[10] Approximately 16% of patients who experience an MI will die within one year of hospitalization. In addition to the substantial burden of mortality, MI is a major contributor to increasing health care expenditures. In 2004, hospitalized MI resulted in approximately $31 billion in inpatient charges. In response to rising costs, the American Heart Association (AHA) recently published recommendations for identifying the most cost-effective treatments for MI as a major priority.[11] A wealth of data from clinical trials and observational studies has led to major advancements in medical care for hospitalized MI. Analyses of National Health and Nutrition Examination Survey (NHANES) data collected between 1980 and 2000 suggest that both in-hospital treatment for MI and secondary preventive therapies have substantially contributed to the decreasing MI death rates.[12] However, the abundance of data on medical treatment for MI has done as much to set the standard of care as it has to diversify it. Furthermore, while there may be substantial support for the efficacy of various medications and procedures as observed in randomized clinical trials (RCT), clinical trial results do not always translate to community-based settings. Additionally, evidence-based treatments may take time to disseminate into clinical practice, and the use of these treatments may vary by provider and geographical area. Monitoring both the patterns of use and outcomes of treated patients as evidence-based therapies disseminate into the

community is important in shaping future clinical decisions and further reducing mortality due to CHD.

II. REVIEW OF THE LITERATURE

II. A. Temporal Trends in Hospitalized MI Event Rates & Medical Therapy for MI

While CHD remains a public health burden in terms of absolute number of events, death rates attributable to CHD have declined in the US since the late 1960s.[13,14] These declines are likely the result of a combination of factors, including changing lifestyle practices and advances in medical treatment approaches.[15-21] A study examining the decline in death due to CHD between 1980-2000 found that nearly half the decrease in CHD mortality was attributable to medical advancements over the past two decades[12]. In addition to changing use of evidence-based medical therapies, recent evidence from several large databases has documented shifts in the demographic makeup, length of stay, and in-hospital management of acute MI patients over the past 30 years.[22-25] Floyd (2009) assessed changes in demographic patterns of 8898 hospitalized acute MI patients in the Worcester Heart Attack Study from 1975 – 2008. Compared with patients hospitalized in 1975, patients in recent years were more likely to be older, female, obese, and have a prior history of diabetes, hypertension, stroke, and heart failure.[13] Investigators also reported a marked decrease in length of hospital stay, with the average length of stay of 17 days in the mid-1970's decreasing to approximately 5 days in 2005. Similar changes in baseline characteristics were documented in the National Registry of Myocardial Infarction (NRMI).[8] As the population ages and the burden of comorbidities increases, in-hospital management of MI becomes more complex. Furthermore, the process of updating guidelines for clinical practice has accelerated, and financial pressures and policy initiatives aimed at utilizing the most cost-effective, evidence-based treatments are continually increasing.[26] Understanding patterns of

implementation and observed utility of emerging therapies in the dynamic clinical environment is integral to effectively improving outcomes for MI patients.

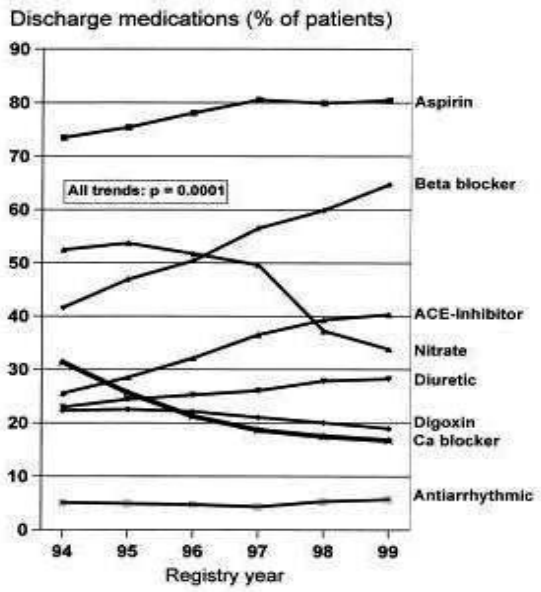
II.A.i Trends in Medications and Procedures for Myocardial Infarction

The availability of medical therapies for in-hospital management of MI is increasing each year.[27] As guidelines are published and revised, more effective therapies become available, and additional data from clinical trials and observational studies confirms their efficacy, rates of medication and procedure use in clinical practice change. Reports from large databases have enhanced our understanding of evolving patterns of treatment for MI.

II.A.i.a Trends in Medications

Patterns of medication use during in-hospital treatment for MI and at hospital discharge have undergone significant changes over the past decades. Data from the Minnesota Heart Survey documented major changes in age and severity-adjusted use of evidence-based medications from 1985 – 1995. Aspirin, heparin, beta-blocker, and angiotensin-converting enzyme (ACE) inhibitor use all increased markedly throughout the study period. Decreases were reported in utilization rates of both calcium channel blockers (CCB) and lidocaine.[28]

Figure 2.1. Trends in Medication Use at Discharge (1990-1999) in the NRMI. [8]

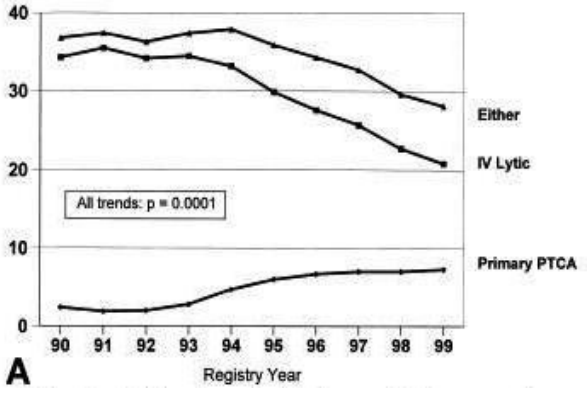


Temporal trends in treatment and outcome for myocardial infarction were analyzed using data from 1.5 million patients in the National Registry of Myocardial Infarction 1,2, and 3, which currently enrolls patients from over one quarter of acute care hospitals in the US.[8] The use of beta-blockers, aspirin, ACE inhibitors, and non-aspirin anti-platelets all increased during the first 24 hours of hospitalization, as well at hospital discharge. In-hospital mortality also decreased over the study period (11.2% to 9.4%). The Worcester Heart Attack Study documented similar declines in CCB and increases in ACE inhibitors and beta-blockers.[29] However, the results of these studies have several important limitations. The Worcester Heart Attack Study was limited to white participants, so trend estimates may not be generalizable to racially heterogeneous populations. NRMI is a large, nationwide registry, but is likely more reflective of practice patterns of larger centers.[30] Additionally, there is no independent validation of registry data. Finally, NRMI does not collect data on follow-up beyond hospital discharge, limiting the ability to make conclusions about outcomes after hospitalization.

II.A.i.b Trends in Revascularization Procedures

The development of revascularization procedures for use during hospitalization represents one of the most significant scientific advancements in the treatment of MI. A number of reports on revascularization trends suggest that use of fibrinolytics and coronary artery bypass grafting (CABG) for hospitalized acute MI is decreasing, while use of PCI, especially with stents, is increasing. Results from the NRMI report that during 1990-1999, use of IV thrombolytics declined (34.3% to

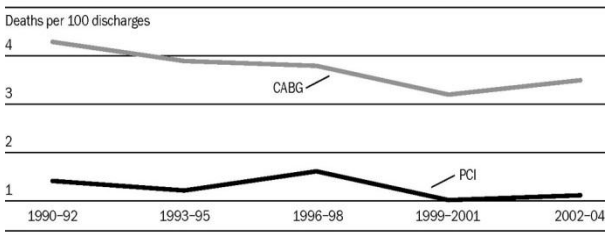
Figure 2.2. Trends in Reperfusion Therapy (1990-1999) in the NRMI. [8]



20.8%) but rates of primary angioplasty increased (2.4% to 7.3%).[8] In an analysis of therapeutic coronary procedures performed between 1990 and 2004 in Olmsted County, Minnesota, investigators reported a sustained increase in percutaneous coronary interventions (PCI) (69%; 95% CI: 43% to 101%), as well as a stabilization, followed by a decline (-33%; 95% CI: -16% to -47%) in CABG.[31] PCI use increased most dramatically in the elderly and in women. Similar patterns were reported in MI patients in Washington State.[22]

Recent data from the Acute Care Tracker (ACTracker) database, which contains administrative records on approximately 6 million discharges per year from 458 hospitals in the US, suggest that total revascularization procedures may be declining. Overall adjusted coronary revascularization procedure rates (per 100000) declined from 382 in 2002 to 358 in 2005. Rates of PCI increased slightly during the study period (264 in 2002 to 267 in 2005), while rates of CABG decreased (121 in 2002 to 94 in 2005).[32] However, because ACTracker utilizes administrative data, specificity is likely to be higher than sensitivity, increasing the potential for undercounting of procedures. Similar results were documented in the NRMI, which indicated a decrease in overall use of reperfusion (either PCI or thrombolytics), from 36.8% in 1990 to 28.1% in 1999. There was a simultaneous decrease in the percentage of patients presenting with Q-wave infarction or left bundle branch block (LBBB) within 12 hours of symptom onset (36.4% in 1994 to 27.1% in 1999). Among these patients, the use of PCI or thrombolytics increased slightly (68.8% to 70%), suggesting that declines in overall use of reperfusion may be due to decreases in the proportion of eligible patients (patients presenting with

Figure 2.3. Temporal trends in in-hospital mortality by revascularization procedure in the NHDS (1990-2004)[7].



Q-wave infarction or LBBB within 12 hours) rather than increasing failure to treat eligible patients. Thrombolytic use in this population increased from 1985-1990 but remained stable thereafter. Rates of CABG doubled in men throughout the study period but remained stable in women.[28]

Investigators recently examined NHDS data (1990-2004) for trends in PCI and CABG use as well as in-hospital mortality by reperfusion strategy.[7] Rates of PCI use (per 10 000 patients) increased from 37.2 patients in 1990-1992 to 59.2 for patients in 2002-2004, a 58% increase. Rates of CABG use initially increased from 34.1 in 1990-1992 to 39.1 in 1996-1998 before decreasing to 25.2 in 2002- 2004. Both CABG and PCI discharge rates were substantially higher for males than for females throughout the study period, with trends in use similar for both males and females. In hospital-mortality rates (deaths/100 discharges) declined from 4.3 to 3.5 for CABG patients during the 15 year interval, but remained stable for patients undergoing PCI. The greatest decrease in mortality rates for CABG patients was seen in women.

While most trend analyses have reported increases in the rate of PCI use over time, the specific type of PCI performed has also changed as new medical technologies, such as stents, have become available. The first bare-metal stent (BMS) was approved for use in the U.S. in 1994, and their use quickly rose throughout the 1990's. A cross-sectional study of Medicare patients from 1993-2001, Lucas (2006) observed marked growth in PCI use (6 to 12 per 1000 beneficiaries),[33] with a 7-fold increase in use of stents since 1995. As the use of stents increased, the rates of repeat revascularization procedures during the subsequent 6 months decreased. Although the development of BMS improved the safety of PCI, restenosis still occurred in a substantial proportion of patients undergoing the procedure. The approval of drug-eluting stents (DES) in 2003 has helped to alleviate this problem,[34] but there is still some concern about the

association between DES and late-stent thrombosis, with several recent studies reporting increased risk of late-stent thrombosis in patients treated with DES.[35-37] Understanding changes in practice patterns as new revascularization procedures are developed and existing technologies are improved can inform efforts to increase utilization of the most cost-effective and beneficial therapies for MI.

Although these and other analyses have helped to characterize temporal patterns of treatment for MI, there are several important limitations to the findings of these studies that are worth noting. First, many trend analyses are limited to short-term (<5 years) of data. Because innovative medical therapies may take years to disseminate into clinical practice, a longer window of time provides a more comprehensive perspective of the temporal patterns of treatment. Second, several were limited to one state or geographic area, limiting the generalizability to other regions of the country. Finally, many of these studies have used a naïve linear trend test to examine the changes in medication use over time. While useful in gaining a broad understanding of changes in treatment use, this test does not provide a detailed picture of the dynamic nature of medical innovation, as the use of many medical therapies follow non-linear trends. The proposed study will provide an important perspective on trends in medication and procedure use in 4 U.S. communities over 20 years, with specific aims of understanding any departure from linearity in trend estimation. For more details on the methodology of the current study, please see Section III.

II. B. In-Hospital Interventions

A wealth of data from clinical trials and observational studies has contributed to improvements in hospitalized MI outcomes over the past 30 years. Analyses of survival associated with a number of pharmacological interventions (aspirin, beta-blockers, ACE-inhibitors, calcium-channel blockers, heparin, non-aspirin anti-platelets, and statins) and

reperfusion strategies (fibrinolytic therapy, PCI, and CABG) have informed the process medical management for MI and contributed to improved patient outcomes after hospital discharge.

II. B. i. Pharmacological Treatment for MI

II. B. i.a Anti-platelets

II. B. i.a.1 Aspirin

Aspirin has been used to treat a variety of anti-inflammatory conditions since the late 1890's, but its anti-platelet properties were not discovered until the 1960's[38]. The clinical utility of aspirin for patients with MI lies in its ability to induce a rapid anti-thrombotic effect by inhibiting production of thromboxane A2, a cyclic prostanoid that increases platelet aggregation. The benefits of aspirin use for acute ST-elevation myocardial infarction (STEMI) were unequivocally demonstrated in the Second International Study of Infarct Survival (ISIS-2).[39] Patients were randomized to receive daily aspirin, IV streptokinase, both, or neither. Investigators reported absolute risk difference in 35-day mortality of 2.4% (relative risk reduction 23%) for aspirin alone, and an absolute risk difference of 5.2% (RRR of 42%) for aspirin combined with streptokinase.

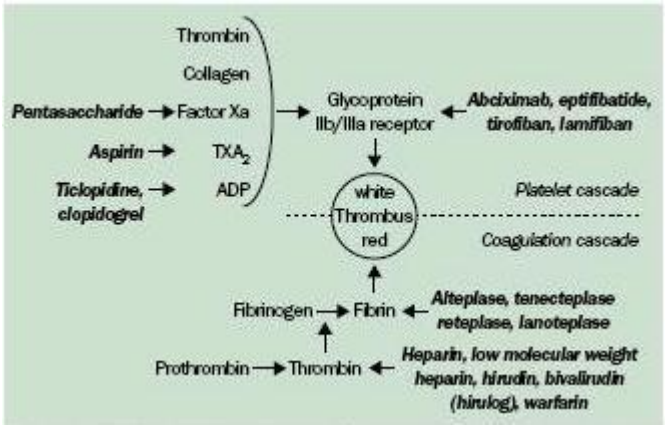
Aspirin use in MI patients has been associated with a reduced risk of composite endpoints (death or reinfarction),[40,41] and reduced rates of coronary reocclusion and recurrent ischemic events after administration of streptokinase or alteplase.[42] In a collaborative meta-analysis of 287 studies involving 135,000 patients in comparisons of antiplatelet therapy versus control and 77,000 comparing different anti-platelet regimens, aspirin reduced non-fatal MI by 1/3, non-fatal stroke by ¼, and vascular mortality by 1/6.[43] Because of data from these and other studies, the AHA has issued Class1A recommendations that aspirin should be administered to patients presenting with STEMI

within the first 24 hours of hospitalization and at hospital discharge.[44] In patients with contraindications to aspirin, Warfarin may be used as an anti-thrombotic agent. A meta-analysis of warfarin use in CAD patients found that warfarin (high or moderate intensity) plus aspirin seemed to confer greater benefit than aspirin alone.[45] However, the translation of these results to community-based practice has not been well-documented.

II. B. i.a.2 Non-aspirin anti-platelets

Platelet aggregation in MI is a complex process, operating through a number of distinct pathways and cascades. The aggregation process is inhibited only in part by aspirin, which acts primarily by blocking the thromboxane-mediated pathway (Figure 2.4). Because of this, new anti-platelet drugs that target other aggregation pathways, including Clopidogrel and glycoprotein IIa/IIIb inhibitors, have been increasingly utilized in the management of MI (Figure 2.1). Several recent clinical trials support the use of clopidogrel in addition to standard in-hospital therapy for MI. In the COMMIT trial, 45800 patients were randomly allocated clopidogrel or placebo in addition to a daily aspirin regimen. Investigators reported a 9% reduction in death, reinfarction, or stroke in STEMI patients.[46] Evidence from the CLARITY-TIMI 28 trial suggests that addition of Clopidogrel to a regimen of aspirin, heparin, and thrombolytics reduced the risk of a composite endpoint of TIMI grade 0 or 1 flow, death or reinfarction.[47] However, the treatment and control groups did not differ in rates of death

Figure 2.4. Coagulation cascade and thrombin formation during acute MI**.** [4]



or reinfarction, and it is not clear whether greater TIMI flow translates to mortality benefits.[48]

Currently, little evidence exists supporting the use of glycoprotein IIb/IIIa inhibitors as the sole means of reperfusion, as they do not appear to restore TIMI 3 flow in the majority of patients.[49] However, the combination of fibrinolytics (half-dose reteplase or tenecteplase) and abciximab is currently recommended for prevention of reinfarction and other complications of STEMI in patients with anterior MI, who are younger than 75 years, and who have no major risk factors for bleeding. In two clinical trials of combination reperfusion, and ASSENT, combination therapy resulted in reduced rates of MI and other complications (GUSTO-V)[50] and reduced reinfarction and refractory ischemia (ASSENT).[51] However, the prevention of reinfarction did not translate into a survival benefit at either 30 days or 1 year. In a meta-analysis of 11 trials involving 27115 patients, de Luca (2005) reported reductions in short- and long-term PCI patients, but not in patients receiving fibrinolytic therapy.[52] In the Atherosclerosis Risk In Communities (ARIC) study, non-aspirin anti-platelet drugs are classified into a one group, so these therapies will be evaluated as a single treatment group. For further discussion on fibrinolytics and ancillary therapy, please see Section 1.5.2.1.2.

II. B. i.b Beta-blockers

The American Heart Association class 1A recommendations for oral beta-blocker (BB) therapy suggest that BBs should be promptly administered to non-contraindicated patients, irrespective of fibrinolytic therapy or PCI. When administered within several hours of STEMI onset, BBs reduce systemic arterial pressure, heart rate, and myocardial contractility, thereby reducing oxygen demand in the myocardium. BBs have been shown favorably influence infarct size in subjects not receiving fibrinolytic therapy, and to reduce the rate of reinfarction in subjects receiving fibrinolytic therapy.

Mortality benefits associated with beta-blocker therapy prior to the fibrinolytic era have been documented. In an analysis of 16000 MI patients with suspected MI, immediate atenolol followed by oral atenolol resulted in a 7-day mortality reduction compared to those not receiving atenolol (4.3% vs. 3.7%).[53] Results from the MIAMI trial, in which 5700 acute MI patients were randomly assigned to metoprolol or placebo, report significantly lower 15-day mortality in patients receiving metaprolol (4.3%) than in those receiving placebo (4.7%).[54] However, the mortality benefit associated with the routine use of IV-BB early in the course of hospitalization has been challenged by several subsequent studies. In a post-hoc analysis of atenolol use in the GUSTO-I trial, a significant mortality benefit was not observed in patients.[55] Additionally, a systematic review of early BB therapy did not document a significant mortality reduction in HF patients.[56] Finally, results from a large clinical trial conducted in China (n=45,852) did not report lower incidence of a composite endpoint of death, reinfarction, or cardiac arrest in patients receiving early metoprolol compared to those receiving placebo.[57] The utility of BB therapy as an immediate, early therapy for MI is unclear.

Heart failure patients and patients in cardiogenic shock represent a special population of patients with regard to the use of beta-blocker therapy. Data from two recent trials underscore the risk of early beta blocker administration to patients with severe heart failure or cardiogenic shock.[58,59] As a result, the AHA recommends oral BB use during the first two days of STEMI hospitalization for hypertensive patients not at increased risk for cardiogenic shock.[44] Additionally, the presence of moderate LV failure early in the course of STEMI precludes the use of early IV beta-blockade until the heart failure has been compensated. However, long-term BB use is strongly recommended for these patients once HF has compensated and/or shock has stabilized.

As the use of PCI in MI increases, examinations of outcomes associated with various medical therapies in patients who are also undergoing angioplasty are becoming increasingly important. The relationship between post-discharge outcomes in patients receiving both beta-blocker therapy and PCI has not been well-documented. To date, no randomized trials examining the use of BB therapy and PCI have been conducted. A pooled study of 2442 patients who underwent successful primary PCI in 4 clinical trials compared rates of death and adverse cardiac events at 6 months reported lower 6 month mortality among PCI patients receiving BB therapy than in those who did not (OR=0.43; 0.26, 0.73), with the greatest benefit observed in patients with a low EF or multi-vessel CAD.[60] However, data from the CAPRICORN trial indicate a benefit of BB therapy in patients with transient or sustained post-infarction LV dysfunction in both PCI and fibrinolytic patients.[61] Nevertheless, these results have not been replicated in community-based settings. The current study will examine survival associated with BB therapy within strata of revascularization to determine what, if any, increases in survival are associated with BB use in PCI patients.

II. B. i. c Calcium-channel blockers

Calcium channel blockers (CCBs) were the most commonly prescribed anti-hypertensive drug in 1995.[62] CCBs block voltage-gated calcium channels in blood vessels and cardiac muscle, thereby reducing muscle contraction, increasing vasodilation, and decreasing blood pressure. However, the effect of early CCB use in hospitalized MI on mortality has been called into question. In an analysis of 19000 patients in 28 randomized trials, investigators did find evidence of a beneficial effect of CCB on mortality (OR = 1.06, 0.96 – 1.18).[63] Similar results were observed among trials involving the acute phase and among longer-term trials following patients up to 2 years.[64-67] In a clinical review of pharmacological strategies secondary prevention for

acute MI, investigators concluded that immediate-release Nifedipine does not reduce mortality or reinfarction in MI patients, regardless of demographic or clinical characteristics, and whether the patient also received fibrinolytic therapy, and may be harmful in patients who are hypotensive or tachycardic.[68]

While overall results from a number of RCTS of CCBs have not reported mortality benefits, immediate-release verapamil given several days after acute MI in patients with preserved LV function who were not eligible for beta blockers was found to reduce incidence of a composite endpoint of reinfarction or death.[69-71] Results from two clinical trials suggest that patients with non-Q-wave MI or with Q-wave infarction and preserved LV function may benefit from diltiazem therapy; however, 53% of placebo patients and 55% of treatment patients in one of these trials also received beta-blocker therapy, which may have confounded results.[70,72] Results from the more recent INTERCEPT trial did not report decreases in cumulative incidence on cardiac death, but did report reductions in non-fatal cardiac events, such as the need for myocardial revascularization.[73]

The ALLHAT trial randomized high-risk hypertensive patients to a CCB, an ACE inhibitor, an alpha-blocker, or a diuretic.[74] The primary outcome (fatal CHD or non-fatal MI) occurred at similar rates in all treatment groups. However, the CCB treatment arm was associated with higher 5-year systolic BP and rates of HF than the diuretic treatment arm, leading investigators to conclude that thiazide-type diuretics are less expensive as well as superior in preventing 1 or more major forms of CVD than CCBs. The additional benefits offered by CCBs to MI patients in the era of aspirin and beta-blockade are unclear.

II. B. i. d IV heparin

Intravenous (IV) heparin has been used in management of acute MI for nearly 40 years.[75] The use of fibrinolytics results in activation of the coagulation cascade, which leads to production of thrombin and fibrin strand deposition. Because of this, ancillary therapy used specifically to inhibit this cascade in patients undergoing reperfusion is integral in preventing re-infarction.[76] IV heparin functions as an antithrombotic that inhibits the coagulation cascade by inactivating thrombin and other proteases involved in blood clotting. However, the marginal utility of IV heparin in conjunction with select reperfusion therapies may vary by the type of fibrinolytic used. Non-specific fibrinolytic agents (streptokinase, anistreplase, and urokinase) are themselves anti-coagulants, and thus, at least conceptually, diminish the rationale for concomitant anticoagulation with IV heparin. However, streptokinase specifically has been shown to induce plasmin-mediated thrombin activity, which increases procoagulant potential and has been cited as rationale for concomitant use of IV heparin.[77]

In ISIS-3, 41,000 patients receiving streptokinase, anistreplase, or alteplase were randomly assigned to heparin or no routine heparin. A small reduction in mortality was observed during the heparin administration period (4 to 5 lives saved per 1000 treated), after which the number of lives saved decreased to 2 to 3 per 1000 and was no longer statistically significant.[78] Similar reductions in mortality associated with heparin use were observed in a meta-analysis of 68000 patients treated with streptokinase with or without heparin.[79] In 2004, the AHA published Class IC recommendations that PCI and CABG patients should receive UFH, and Class IB recommendations that IV heparin should be given to patients treated with non-selective fibrinolytic agents who experience large or anterior MI, atrial fibrillation, previous embolus, or known LV thrombus.[44] The magnitude of additional benefit conferred by heparin use in the fibrinolytic era is not clear.

II. B. i. e ACE inhibitors

In an overview of data from 4 randomized trials (CONSENSUS-II, CCS, ISIS, SMILE) comprising 98496 patients with ACE inhibitor therapy started in acute phase (0 to 36 hours) & continued for 4 to 6 weeks was associated with a decrease in 30-day mortality (7.1% in treatment group versus 7.6% in control group).[80] This mortality reduction translated to an absolute benefit of 4.6 fewer deaths per 1000 patients. In the ISIS-4 trial, the largest relative benefit was seen in days 0-1 (44 fewer deaths compared to controls) and in days 2-7 (37 fewer deaths), demonstrating the importance of early therapy.[81] The mortality benefit of ACE inhibitors appears to be particularly large in high-risk patients (Killip class 2 or 3, heart rate >=100 bpm on admission), and in patients 55 to 74 years of age, with anterior infarct, or presenting with pulse rate of 80 bmp or higher. For patients contraindicated to ACE inhibitors, angiotensin receptor blockers (ARBs) may be administered. ARBs have shown similar mortality benefits to ACE-inhibitors in MI patients who also have residual LV dysfunction.[82] In 2006, the ACC/AHA added ARBs to the performance measure for ACE-inhibitors in LVSD patients, indicating that ARBs were an “effective alternative therapy’ for patients with LVSD and contraindications to ACE-inhibitors.[83] The ARIC study collects data on ACE-inhibitors and ARBs in a single question (“ACE or Angiotensin II inhibitors”). Thus, ARBs and ACE-inhibitors will be assessed as a single medication group.

II. B. i. f Statins

Statin use, both during the initial MI hospitalization and after discharge, reduces the risk of death in patients with coronary artery disease. The widespread use of statins in patients at risk for cardiovascular events is a recent development. Results from the first major study documenting a beneficial effect of statins in patients at risk for CHD were published in 1994.[84] A 42% reduction in CHD mortality was documented in 4444 patients

with moderate hypercholesterolemia the Scandinavian Simvastatin Survival Study. Interestingly, similar mortality reductions were reported among groups with the lowest quartile and the highest quartile LDL-C, suggesting that Statins may be effective in reducing CHD mortality even in patients with mild to moderate hypercholesterolemia.

In the CARE Trial, 4159 patients with a history of MI and mean cholesterol values similar to those of the U.S. population were randomly assigned to pravastatin or placebo. Investigators reported a 24% relative risk reduction in adverse events (fatal CHD and non-fatal MI) over a period of 5 years.[85] Similar relative risk reductions were reported in the lipid study, which was stopped prematurely because of the observed efficacy of prevastatin in reduction of CHD mortality, total mortality, and stroke.[86] Smaller reductions in mortality were reported in the Heart Protection Study, which documented the largest decreases in total mortality in women, the elderly, and subjects with a baseline LDL-C of <100 mg.dl.[87]

While early trials of statin therapy have focused on patients initiating statin treatment regimens 4 to 6 months after hospital discharge, newer studies have evaluated the benefits of statin use during the acute phase of MI. The Lipid-Coronary Artery Disease Trial randomized 126 patients with CAD to early pravastatin treatment or usual care. Compared to the usual care group, patients treated with pravastatin had fewer clinical events 2 years after discharge.[88] In the MIRACL trial, 3086 patients admitted for ACS were randomized to atorvastatin or placebo within 4 days of admission. The risk of a composite endpoint of death, non-fatal MI, resuscitated cardiac arrest, or recurrent severe ischemia was significantly lower in the atorvastatin patients (14.8%) than in the placebo patients (17.4%).[89] In a prospective cohort study of 20000 ACS patients in Sweden, Stenestrand, et al (2001) documented a 25% reduction in 1-year mortality among patients treated with statins.[90]

Results from some trials support the use of intensive statin therapy over moderate or conservative statin therapy. The PROVE-IT (TIMI-22) trial randomized 4162 patients to intensive (80 mg/dl) vs. moderate (40 mg/dl) therapy within 10 days of hospital admission. Reductions were documented in 2-year risk of a composite endpoint (all-cause mortality, recurrent MI, and stroke) in patients undergoing intensive therapy (22.4%) compared to those undergoing moderate therapy (26.3%).[91] Favorable trends in all-cause mortality trial and intensive statin use were also documented in the A to Z trial, but these estimates did not reach statistical significance.[92]

Statin use is contraindicated in patients with liver disease and patients who are pregnant. Despite strong support for statin use from national guidelines, low number of contraindications, and rarity of serious side effects, actual use of statins after MI varies, with 20% of patients discontinuing use within a month after hospital discharge[93] and 30% discontinuing use after 1 year.[94,95] Patterns of statin adherence and their resultant impact on mortality will be explored in the proposed project. For more information on classification of statin adherence, please see section 1.8.

II. B. ii Reperfusion Procedures

II. B. ii. a Fibrinolytics

Fibrinolytics confer a mortality benefit to STEMI patients by reducing infarct size, thereby salvaging healthy myocardium; favorably influencing infarct healing and myocardial remodeling; and reducing the potential for ventricular arrhythmia.[96] However, these effects appear to be time-dependent, with most RCTs demonstrating benefits only when fibrinolytics are administered within 12 hours. The AHA Class IA recommendation regarding fibrinolytics suggests that, in non-contraindicated patients, fibrinolytics should be administered to STEMI patients within 12 hours of symptom onset who have ST

elevation greater than 0.1 mV in at least 2 contiguous precordial leads or 2 adjacent limb leads.

The mortality benefit of fibrinolytics in MI patients has been well-established in a number of large clinical trials, inluding the GISSI, ISIS-2, the AIMS study, and the ASSET trial.[39,97-99] In a 1994 overview of 58,600 patients in 9 clinical trials of fibrinolytic therapy vs. control, investigators found a 21% relative reduction in 35-day mortality in STEMI patients.[100] The greatest mortality benefit was observed within the first hour of symptom onset, with a decrease in benefit of 1.6 per 1000 patients for every one hour delay. The mortality reduction associated with fibrinolytic therapy has been observed regardless of important covariates (including sex, history of diabetes, BP, heart rate [<180 mm HG]), or history of previous MI.

II. B. ii. a Types of fibrinolytic therapy

Data from the Gusto-I[101] and Gusto-III[102] trials suggest that accelerated alteplase and reteplase with IV heparin may be more effective in achieving early reperfusion over streptokinase. However, these therapies are more expensive and confer slightly greater risk of ICH. The ARIC surveillance study collects data on a single question documenting whether the patient received streptokinase, urokinase, anistreplase, APSAC, or TPA reperfusion.

II. B. ii. b Combination therapy

While the development fibrinolytic therapy has undoubtedly improved MI patient outcomes, it has 3 important physiological caveats worth noting: 1) the targeted thrombus can break apart into smaller pieces, resulting in microembolisation; 2) the fibrinolytic targets only the fibrin-rich part of the thrombus, leaving the platelet-rich portion unaffected; and 3) fibrinolysis leads to increased free thrombin and activates

platelet aggregation. Because of this, fibrinolytics are used in conjunction with an aggressive anti-platelet regimen.

Aspirin is a weak anti-platelet agent, inhibiting only one of several platelet aggregation pathways. Thus, non-aspiring anti-platelets are often used, specifically those that inhibit the platelet glycoprotein IIb/IIIa. The use of GP IIB/IIIA inhibitors in acute MI is supported by evidence from a number of clinical trials indicating more complete reperfusion[103-106] and shorter times to ST-segment resolution[107,108] than fibrinolytic therapy alone.

Because thrombin is released from the thrombus during fibrinolytic therapy, antithrombin agents such as heparin may be administered to patients receiving pharmacologic reperfusion. However, reports from several large trials did not document significant reductions in 30-day mortality or reinfarction among patients given heparin compared to those given placebo.[78,109] Additionally, investigators reported increases in major bleeding complications. Despite the lack of reported mortality benefits, unfractionated heparin is still commonly given to patients receiving streptokinase.

II. B. ii. b Percutaneous Coronary Intervention (PCI)

Percutaneous Coronary Intervention (PCI) is a highly-effective mechanical revascularization procedure that has been used in hospitalized MI patients in the US for 25 years. PCI involves the inflation of a balloon catheter at the site of a thrombotic occlusion in an infarct-related artery, with or without the placement of a stent. When performed in a timely fashion in eligible patients, PCI results in reestablished TIMI-2 flow range from 70%-90%.[110-112]

PCI is especially useful in patients who are at high risk for reinfarction,[113] for whom fibrinolysis is not successful,[114,115] and for patients who are contraindicated to

fibrinolysis.[116] However, PCI administration is dependent on both the availability of skilled staff and the time window since symptom onset. The AHA recommends that, if immediately available, primary PCI should be performed in a timely fashion (within 90 minutes of symptom onset) by persons who are skilled in the procedure (perform more than 75 PCI procedures per year) in a supported laboratory environment (performs more than 200 PCI procedures per year). If the expected additional time needed for PCI administration compared to fibrinolytic administration is greater than 1 hour, fibrinolytics are preferred. However, if the symptom duration on presentation is more than 3 hours, PCI should be performed.[44]

Because so few facilities are equipped with the resources necessary to successfully administer PCI, patients presenting to non-PCI capable facilities are often transferred to PCI-capable facilities for the procedure. It is still unclear whether the increased delay associated with transfer to a PCI-capable facility is merited by the relative benefit of PCI. Results from the DANAMI-2 trial suggest that patients who present to centers without cardiology capabilities had better outcomes with transfer for PCI than with fibrinolytic treatment at the presenting hospital, but these results have not yet been replicated.[117]

II. B. ii. b. 1 Stents

Stent use for MI has increased markedly in the past decade following the publication of results from several clinical trials. In a 1999 study by Grines and colleagues, 900 MI patients were randomly assigned to angioplasty with stenting or angioplasty alone. Investigators reported several benefits associated with stenting, including decreased rates of prevalence of angina and lower occurrence of a combined endpoint of death, reinfarction, disabling stroke, or need for target-vessel revascularization. However, according to study investigators, the decrease in the combined endpoint was “due

entirely to the decreased need for target-vessel revascularization", and mortality rates between the two groups were not statistically different.[110]

Results from another, smaller clinical trial also report better event-free survival at one-year in a systematic stenting group (80.2%) than in a conventional angioplasty group (71.8%).[118] This difference also appeared to be driven by a decreased need for revascularization. Whether the increase in event-free survival associated with stent use that has previously been reported extends to mortality benefits at one year in unclear.

II. B. ii. b. 2 Facilitated PCI

Recent trials have investigated the association between mortality and "facilitated PCI", or PCI performed after fibrinolytics have been administered. In ASSENT-4, a trial of 1667 patients receiving full-dose tenecteplase and PCI versus primary PCI alone,[119] patients who were received fibrinolytics prior to PCI experienced increased rates of in-hospital death compared to those undergoing PCI alone. The FINESSE trial randomized 2452 patients to reduced-dose fibrinolytics plus abciximab alone followed by PCI or placebo. Results from FINESSE found similar rates of a composite endpoint in patients receiving abciximab and reteplase prior to PCI, abciximab alone before PCI, and abciximab alone at the time of PCI.[120] Because these results were reported after the majority of the study period, we do not expect a large number of patients to have undergone both PCI and fibrinolytics; however, if the number of patients undergoing facilitated PCI is substantial and power considerations allow, we will analyze patients receiving both PCI and fibrinolytics as a distinct treatment group.

II. B. ii. c Comparison of PCI and Fibrinolytics

Evidence from clinical trials suggests that for facilities that have PCI capabilities, PCI may be superior to fibrinolysis in preventing adverse outcomes including death, recurrent

MI, or stroke. In a meta-analysis 23 clinical trials comparing PCI to thrombolytics (RR; 95% CI), patients undergoing PCI experienced lower rates of short-term mortality (0.70; 0.58-0.85), less nonfatal reinfarction (0.35; 0.27-0.45), and less hemorrhagic stroke (0.05; 0.006-0.35) than those receiving thrombolytic therapy. However, PCI patients did experience slightly increased rates of major bleeding. (1.3; 1.02-1.65).[121]

Much of the benefit seen in PCI patients appears to be driven by reduced rates of nonfatal recurrent MI. The DANAMI-2 study randomly assigned 1572 patients with >0.4 mV of ST elevation in 2 contiguous leads who arrived to the hospital within 12 hours of symptom onset to PCI or accelerated alteplase. A composite endpoint of death, reinfarction, or stroke within 30 days was documented in 8.5% of PCI patients and 14.2% of fibrinolytic patients.[117] However, the results of this trial have been questioned due to concerns about study methodology, including the use of a combined outcome, the exclusion of diabetics and other high-risk patients, and the low proportion of screened patients that were included in the trial.[122]

Several important caveats regarding the use of PCI in MI are worth noting. First, the mortality benefit of PCI over fibrinolytics decreases as time delay increases, and fibrinolytics can be administered more quickly than PCI.[123] Second, it is estimated that 20% of hospitals nationwide have catheterization labs, and even fewer have the ability to administer primary PCI. The benefit of PCI over fibrinolytics may also vary by hospital size. Lower mortality rates after PCI compared to fibrinolytics have been documented for intermediate and high volume centers, but not for lower volume hospitals.[124] In an analysis of NRMI data, investigators documented an inverse relationship between PCI procedure volume and mortality rates for STEMI patients; this same association was not documented for fibrinolytics.

II. B. ii. d Coronary Artery Bypass Graft (CABG)

Coronary artery bypass grafting (CABG) was first used for acute MI in 1968 and quickly became the treatment of choice for patients with severe coronary disease. However, as advances in technology become available and experience with PCI increases, the additional benefits of CABG for patients with severe coronary disease have been reexamined.[125] Data from a number of clinical trials comparing CABG to PCI with bare metal stents suggest similar survival in the two groups, with increased rates of revascularization at 5 years in PCI patients.[126-128] Results from the SHOCK trial report that, in patients with cardiogenic shock, CABG may confer the same survival benefit as PCI. Among patients experiencing cardiogenic shock who underwent emergency revascularization, the 30 day-mortality rate was 45% for PCI patients and 42% for CABG patients.[129] However, SHOCK investigators acknowledge that the survival benefit of surgery over PCI may not be fully evident before 1 to 5 years after hospitalization. More recent studies have documented a survival benefit for CABG over long-term follow-up, primarily because of the need for fewer repeat revascularizations in CABG patients.[31,130,131] One recent trial did report better event-free survival in the short-term with CABG compared to PCI. The SYNTAX trial randomly assigned 1800 patients with 3 vessel or left main CAD to CABG or PCI.[125] Rates of major adverse cardiac or cerebrovascular events at 1 year were higher in the PCI group than in the CABG group (17.8% vs. 12.4%, respectively). Rates of death and MI were similar in both groups at 1 year.

The AHA has issued a recommendation that revascularization with CABG should be undertaken “if critical anatomy exists”, but that patients who have been stabilized and are not experiencing ongoing ischemic or hemodynamic compromise and who have experienced a significant decrease in LV function should delay surgery to allow for

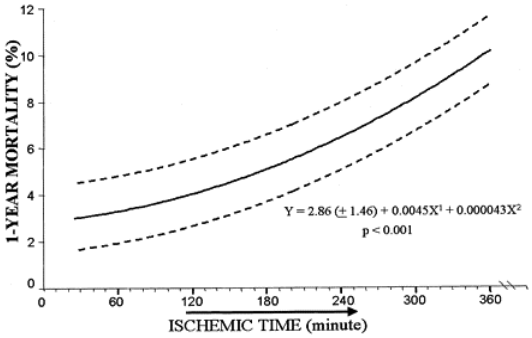
maximum myocardial recovery.[44] CABG is the preferred mode of revascularization in patients with cardiogenic shock who also have triple-vessel or left main disease to unload the heart and achieve complete revascularization.[132]

II. B. ii. e Time to Revascularization

The time elapsed from symptom onset to revascularization is a major predictor of outcomes after acute STEMI.[133-135] Fibrinolytics confer a mortality benefit to STEMI patients by reducing infarct size, thereby salvaging healthy myocardium; favorably influencing infarct healing and myocardial remodeling, and reducing the potential for ventricular arrhythmia.[96] However, these effects appear to be time-dependent, with most RCTs demonstrating benefits only when fibrinolytics are administered within 12 hours.

The current "door-to-needle" recommendation for STEMI patients receiving thrombolytic therapy is 30 minutes, and the "door-to-balloon" recommendation for patients receiving angioplasty is 90 minutes.[44] The time elapsed from symptom onset to initiation of fibrinolytic therapy is a direct predictor of infarct size and patient outcome, and the efficacy of fibrinolytic therapy diminishes with passing time.[133,134] In animal studies, reperfusion at 90 minutes was found to salvage approximately half of the at-risk myocardium.[135]

Figure 2.5. Time-to-treatment and 1-year mortality, 1994 - 2001[6].



The beneficial effects of PCI appear to be less time dependent than those of fibrinolytics.[136,137] For high-risk patients receiving PCI, time since symptom onset may be more predictive of outcomes than for low-risk patients.[138] In an analysis of 27080 patients with STEMI or left-bundle branch block, Cannon, et al. documented increases in adjusted odds of mortality for door-to-balloon times of greater than two hours compared to door-to-balloon times of less than 2 hours.

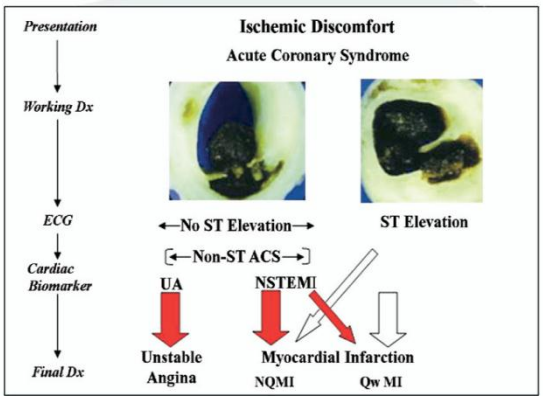
In another observational study of 1791 patients treated by primary angioplasty, each 30-minute delay was associated with an adjusted relative risk for 1 year mortality of 1.08 (1.01 – 1.15).[6] However, shorter balloon times may be a marker of a hospital's general adherence to treatment guidelines or better quality of care, which are themselves associated with survival after hospital discharge.

Shorter time-to-treatment may be differentially beneficial depending on the reperfusion strategy chosen and the time elapsed since symptom onset. Results from the PRAGUE-2 study suggest that for patients who present within 3 hours of symptom onset, mortality is similar between groups receiving PCI and those receiving fibrinolytics.[139] In the CAPTIM trial, however, patients presenting within two hours of symptom onset had improved outcomes with thrombolytics compared with PCI. This effect was reversed when the analysis was restricted to patients arriving beyond 2 hours, suggesting that patients with greater pre-hospital delays may benefit from PCI over fibrinolytics.[140]

II. C Acute MI Subclasses

Beginning in 2000, recommendations for treatment of acute MI were made separately for two diagnostic subclasses: ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI). While STEMI is characterized by an elevation of the ST segment as seen on an ECG, NSTEMI is characterized by ST-depression or T-wave inversion and/or positive biomarkers of necrosis (e.g. troponin) in an "appropriate clinical setting" (eg., with other symptoms such as chest discomfort). As

Figure 2.6. Diagnostic Pathway for STEMI, NSTEMI and UA. [1]



shown in Figure 2.6, NSTEMI patients are typically differentiated from STEMI patients by electrocardiographic readings and from unstable angina patients by biomarker values.

Clinical trials have historically focused on STEMI patients, which may translate to wider availability of STEMI-specific treatment information and more rapid implementation of evidence-based therapies for STEMI patients than for NSTEMI patients over time. However, NSTEMI patients compose the majority of acute MI patients seen in emergency departments,[141] and the development of increasingly-sensitive biomarkers has led to reclassification of a large number of NSTEMI patients who would have previously been diagnosed as unstable angina. Additionally, a number of studies have reported lower rates of medication use and revascularization in NSTEMI patients despite data that supports the use of such therapies.[142,143] As the proportion of MI patients diagnosed as NSTEMI rises, it is important to document patterns in this distinct population's receipt of evidence-based medical treatment during an acute MI event.

Few studies have examined differences in temporal trends in the treatment of patients presenting with STEMI compared to NSTEMI, and published reports have been limited to homogenous populations, short follow-up periods, or convenience samples that are not representative of the population at large. A 2010 analysis of trends in medical treatment for STEMI & NSTEMI patients documented initial disparities in the use of beta-blockers, lipid-lowering therapy, aspirin, and ACE Inhibitors in NSTEMI patients, with narrowing of these trends over time.[142] However, this study was conducted in an all-white population from a single geographic region, limiting generalizability of results to less homogenous populations.

In a 2007 analysis of medical management of 2151 STEMI and NSTEMI patients, Montalescot and colleagues reported similar in-hospital and long-term prognosis among

STEMI and NSTEMI patients.[144] However, NSTEMI patients underwent reperfusion less frequently and with greater time delays than STEMI patients. Data from the National Registry of Myocardial Infarction (1990-2006) reported similar improvements in quality of care over the study period for STEMI and NSTEMI patients.[145]

Recommendations from the update to the AHA guidelines (2007) indicate that the average NSTEMI patient waits at least 2 hours after symptom onset to seek care, and that women affected by NSTEMI wait longer than men. This delay does not appear to have improved over the past decade.[1]

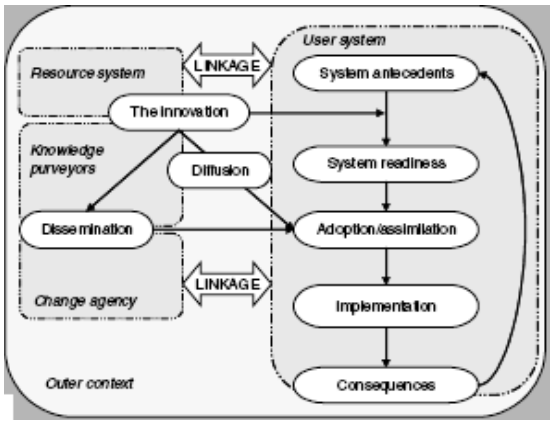
Some evidence suggests a trend in practitioners taking an increasingly aggressive approach with the medical care of NSTEMI patients, such as performing evaluation of LV function, angiography and, if indicated, revascularization within 24 hours of hospital arrival.[142,145] Recent interest has focused on the use of early, invasive strategies for NSTEMI, for example, diagnostic angiography with intent to revascularize without a prior non-invasive stress test or failure to respond to other medical treatment. A number of multicenter trials have shown similar outcomes with initial conservative and invasive strategies, and there may be risk associated with revascularization procedures. A meta-analysis of conservative and invasive strategies for NSTEMI documented better patient outcomes associated with more invasive rather than more conservative strategies.[146] However, these results have not yet been confirmed in population-based settings.

II. D Implementation of Medical Innovation

Evidence provided by both clinical trials and observational studies has significantly contributed to the body of knowledge regarding medication use in MI patients. Clinical guidelines and recommendations for hospitalized MI treatment have been informed by both large observational studies such as ARIC, NRMI, Framingham, and MONICA, as

well as large clinical trials such as COMMIT, ISIS, GISSI, and ASSENT However, the application of such knowledge in clinical practice is an integral step in positively impacting quality of care and improving outcomes in hospitalized MI. The theories of diffusion of innovation and system dynamics have helped to characterize the patterns by which new, evidence-based therapies are implemented in clinical practice.[147-149] Greenhalgh, et al (2004) expanded on these theories and, using results from a comprehensive review of the literature regarding diffusion of innovation in service organizations, developed a useful conceptual model describing the patterns by which change is adopted in service organizations such as medical facilities.[2] Greenhalgh identifies several integral factors in the implementation of such change, including relative advantage (in terms of either medical effectiveness or cost-effectiveness), compatibility with the adopters' needs, the ability to experiment with the innovation on a limited basis, observability of intended benefits, and ability to reinvent or adapt the innovation to suit the adopters' needs (Figure 2.7). Factors influencing implementation of change are said to lie on a continuum between passive diffusion (unplanned, informal, and largely mediated by peers) to active dissemination (centralized, formal, and likely to occur through vertical hierarchies). In the passive diffusion model, evidence from peer-reviewed literature or medical conference presentations is thought to change clinical practice by trickling down along a "pressure gradient", where magnitude of treatment effect and strength of the evidence are more likely to positively influence change in practice.[150] However, several systematic reviews have suggested that typical

Figure 2.7. Conceptual Model of Diffusion, dissemination, and Implementation of Innovation[2].



mechanisms of passive diffusion (attending conferences, browsing journals, listening to lectures) are unlikely to significantly impact clinical practice.[151] Some evidence exists supporting the theory that training physicians to actively seek out and apply knowledge from clinical trials and observational studies can increase the rate of diffusion of innovation into practice.[152] However, there are caveats to this approach, as the process of critically evaluating and applying evidence from the literature is time-consuming and can lead to information overload.[153] Coupled with other barriers to implementation of change, including impaired knowledge or attitudes, group psychology, organizational characteristics, and economic factors, the burden of appropriately adopting medical innovation in a timely fashion often encumbers the translation of research into practice.[149]

Empirical manifestations of these obstacles are well-illustrated in a number of reports on quality of care, guideline adherence, and trends in medication use. In a random telephone survey and medical record review conducted in 12 metropolitan areas in the United States, Mcglynn, et al (2003) reported that patients received only 54.9 percent of recommended care.[154] One analysis of implementation of AHA guidelines for out-of-hospital cardiac arrest found that agencies required an average of 416 days to implement new treatment guidelines.[155] Gaps between evidence and implementation for treatment specific to MI have also been reported. The results of the beta-blocker Heart Attack Trial, published in 1981, reported a significant mortality benefit for MI patients.[156] However, 15 years later, only 62.5% of eligible patients were receiving the drug.[157] A wealth of data from clinical trials supports the use of aspirin both in the acute phase of myocardial infarction and as a method of secondary prevention.[158] However, analyses of two independent samples of office visits to US physicians revealed that even as late as 2000, aspirin was prescribed for at most one third of non-contraindicated patients.[159]

More recent data indicates that this statistic has improved[160] but gaps still exist between available evidence and real-world practice, especially for selected subgroups .[161-166] Obtaining a comprehensive picture of both the rate at which innovations diffuse into medical practice and the factors associated with their implementation or lack thereof is integral in the process of translating research into improvements in quality of care for diverse populations of MI patients.

II. E Clinical trials versus community-based evidence

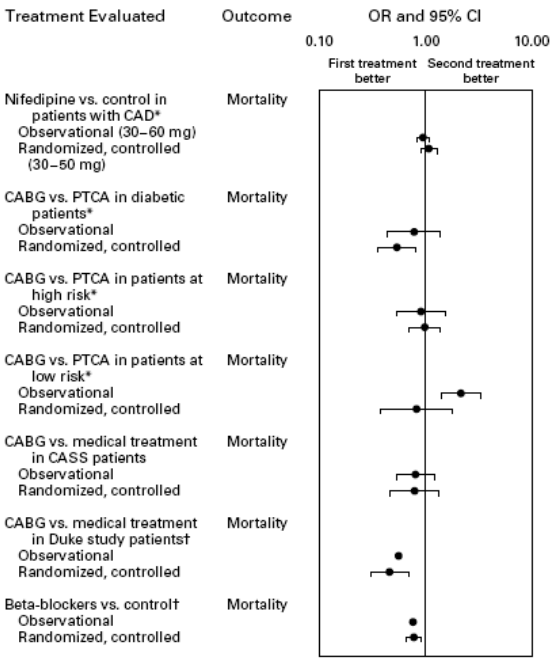
While analyses of trends in treatment patterns of MI rely on observational data, studies of medication use and survival are often structured as randomized clinical trials. The RCT is generally considered the gold standard for causal inference in the study of treatment effects in cardiovascular disease epidemiology.[167,168] However, results from RCTs are not always observed in the general population, and are seldom entirely consistent with results from other clinical trials. Clinical trials have stringent inclusion and exclusion criteria, and thus are not representative of the majority of patients who present to hospitals across the United States. Evidence from several studies indicates that clinical trial populations may not represent how MI patients are treated in actual clinical practice.[169-171] In an analysis of 36 topics with conflicting results from over 200 trials in cardiology and gastroenterology, Horwitz, et al (1987) documented multiple contradictory results in RCTs of cardiovascular treatment and survival. Investigators concluded that inconsistency in RCT results stems from differences in the clinical setting and therapeutic evaluation, including study group selection, baseline variable differences, and management of intermediate outcomes.[172]

Concern about bias introduced by unmeasured confounders has limited the use of data from observational studies in comparative analyses. A number of influential studies conducted in the 1970s and 1980s suggest that positive treatment effects are inflated in

observational studies as compared with RCTs. One study of published results from 145 papers on acute myocardial infarction found that 56% of nonrandomized trials reported positive treatment effects, compared with 30% of blinded RCTs.[173] Another analysis compared results from RCTs and observational studies in 106 studies of 6 different therapies. Of 56 trials with historical controls, 44 (79%) reported a favorable treatment effect, compared with only 10 of 50 (20%) trials employing randomization.[174]

Results from more recent analyses have challenged the belief that treatment effects are usually overestimated in studies using observational data. Benson, et al (2000) compared treatment effects observed in randomized clinical trials and observational studies published from 1985 to 1998.[3] In an analysis of results from 136 articles in 19 treatment areas, the authors reported little evidence of large differences in reported treatment effects between RCTS and observational studies for both cardiologic treatments (Figure 2.8) and treatments in other disease areas.

Figure 2.8. Results of observational studies and randomized, controlled trials of cardiologic treatments[3]



In another analysis of 99 studies in 5 clinical topic areas, Concato, et al (2000) documented “remarkably similar” results between observational studies and RCTs. The authors reported no systematic overestimation of the magnitude of treatment effects between observational studies and RCTs.[175] In another analysis of 18 randomized trials and observational studies in health-services research, McKee, et al (1999) reported that, while treatment effects vary

according to research design, neither the randomized nor the observational methods consistently produced greater magnitude of effects.[176]

The Benson and Concato analyses had several advantages over similar comparisons conducted in the 1970s and 1980s. First, investigators were able to examine treatment effects in a variety of topic areas, including breast cancer, tuberculosis, trauma, and stroke. Second, because the studies used in the Benson and Concato analyses were more recent (1989 – 1998 and 1991-1995, respectively), they may have been able to account for bias using methodology not available in earlier studies. The non-randomized studies in the Chalmers and Sacks studies comprised trials using historical controls and unblinded trials instead of the cohort and case-control studies utilized in the Concato analyses, which may be less prone to the types of systematic bias introduced in the earlier non-randomized trials.

Randomization in controlled trials reduces bias introduced by unmeasured confounders in observational studies. However, contrary to conventional wisdom and as shown by comparisons of multiple results from both observational studies and RCTs, the absence of randomization in observational studies does not consistently result in the overestimation of treatment effects. Well-designed cohort and case-control studies with sophisticated modeling approaches that account for differential underlying mortality risk between treated and untreated patients provide valuable contributions to our knowledge of treatment effects in the general population. In the proposed study, careful inclusion of relevant covariates and the construction of propensity scores to account for likelihood of receiving treatment will minimize bias introduced by underlying differences in treatment groups.

II. E. i Underlying Treatment & Mortality Risk

Patients who receive a particular medication may differ from those who are not on a number of covariates which may, in turn, affect survival probability. Bias may arise when treated subjects differ from untreated subjects on one or more covariates that affect both the likelihood that they will receive the treatment and their underlying survival probability, or baseline risk.[177] In addition to conventional models that control for covariates affecting both probability of medication use and survival, it is possible to calculate scores representing a given patient's exposure propensity and underlying risk of the outcome of interest to account for such differences.

II. E. i. a Disease Risk Scores

In analyses of patient outcomes by medication, the use of efficient, risk-adjusted methods can substantially increase validity of study results. Disease risk scores (DRS) use clinical data to quantify underlying mortality or recurrent MI risk in a summary score, which is then treated as a confounder and controlled for in regression models. The Predicting Risk of Death in Cardiac Disease Tool (PREDICT) score was developed using 30-day, 2-year, and 6-year mortality data from the Minnesota Heart Survey.[178] The score is a validated metric that predicts mortality in ACS patients from clinical presentation data, including cardiogenic shock, history of MI or cardiac procedures, age, severity of electrocardiographic changes, congestive heart failure, and Charlson Comorbidity Index. The PREDICT score has performed well in analyses of mortality in all three endpoints, with C-statistics in the range of 0.76 – 0.77. In a comparison of Thrombolysis in Myocardial Infarction (TIMI) and PREDICT scores among MI patients in Olmstead County, the PREDICT score showed consistently better discriminant accuracy than did the TIMI score, regardless of time point or reperfusion strategy.[179]

II. E. i. b Exposure Propensity Scores (PS)

PS represent 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. In randomized controlled trials, random assignment of subjects to treatment or control groups tends to balance the distribution of these covariates between the two groups. Because randomization is not possible in observational studies, a method called the propensity score may be utilized to construct matched sets or strata of subjects that tend to balance the distribution of covariates included in the score. This "virtual randomization" has been shown to result in equal distribution of included covariates in treated and untreated patients,[180] with a number of simulation studies reporting comparable covariate distribution among groups after scores are calculated.

II. E. i. c PS versus DRS

Sturmer (2005) evaluated the behavior of DRS, PS, and conventional models in an analysis of NSAID use and all-cause mortality in Medicare beneficiaries.[181] Investigators did not report major differences in the performance of PS, DRS, or conventional models in this population, even when using larger p-values for covariate inclusion for PS and DRS than for conventional models. However, there is some evidence that PS performs better (provides greater observed reduction of confounding) than conventional models when the outcome is rare (fewer than eight outcomes per included covariate)[182] and better than DRS when the exposure is prevalent and the outcome is rare.[183] In the proposed study population, we expect to have varying numbers of deaths depending on the cutpoint used (28-day or 1 year) and on the therapy used. Thus, we plan to evaluate both DRS and PS as potential effect-measure modifiers and confounders in trend and survival analyses.

III. METHODS

III.A Study Population

The design of the community surveillance component of the Atherosclerosis Risk in Communities (ARIC) study has been described. Briefly, it is a continuous retrospective surveillance study of hospitalized coronary heart disease (CHD) events with mortality follow-up designed to estimate trends in CHD incidence and mortality using standardized criteria and methods in four U.S communities: Forsyth County, North Carolina; Jackson, Mississippi; eight suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Eligible events included inpatient and out-of-hospital deaths due to CHD and hospitalized nonfatal MI 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 reported12. Trained abstractors investigate hospitalizations randomly sampled from annual discharge lists obtained from each hospital serving the four ARIC communities. Events were 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 were reviewed, and relevant clinical information was abstracted onto standardized forms. Collected data items included presenting symptoms; timing of symptom onset; history of MI, angina, and other cardiovascular conditions; in-hospital medications, diagnostics, and medical procedures; laboratory values for a number of relevant cardiac biomarkers; and up to 3 sets of twelve-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 Center were utilized to ensure reproducibility.

III. B MI diagnostics

A computerized algorithm using electrocardiogram readings, history of chest pain, and cardiac biomarker levels (total creatinine phosphokinase(CK), creatinine phosophokinase-myocardial band (CK-MB), lactate dehydrogenase (LDH), troponin I, and troponin T) was used to assign an MI diagnosis to sampled hospitalized events. Using this algorithm, events were classified as one of the following: 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 elevation MI using pain presentation and Minnesota-coded electrocardiogram data from the first, third, or last ECG performed during hospitalization. Multiple hospitalizations occurring within 28 days were combined and treated as one event. Any event requiring review (for example, events where the computer-derived classification of definite MI disagreed with the ICD-9-CM codes for discharge diagnosis) was independently classified by two trained reviewers. Any disagreements in diagnoses were then adjudicated by a third reviewer.

The ARIC study has classified myocardial infarction events into STEMI and NSTEMI using Minnesota coded electrocardiograms for all definite and probable MI events using variables in the SECA data file. Pain presentation and selected ECG variables are used to determine STEMI/NSTEMI status. For more information on STEMI/NSTEMI coding in ARIC, please see Appendix V.

III.B.i Quality Assurance for ascertainment

Case ascertainment for hospitalized MI was assessed using a review of computerized criteria used to identify eligible cases. Two-day training sessions were held annually to standardize medical record abstracting, and abstractors were certified after successful completion of the certification exercises. 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 Center were utilized to ensure reproducibility. Blinded repeat codings of ECG readings from all cohort participants were compared by the Collaborative Studies Coordinating Center (CSCC).

III.B.ii Quality assurance for Diagnostics

Any event requiring review (for example, events where the computer-derived classification of definite MI disagreed with the ICD-9-CM codes for discharge diagnosis) were independently classified by two trained reviewers from the Mortality and Morbidity Classification Committee (MMCC). Any disagreements in diagnoses were then adjudicated by the MMCC chairman.

III.B.iii Sampling

The ARIC surveillance study uses various sampling procedures for identifying eligible deaths for investigation and eligible hospitalized cases for investigation. Sampling is a stratified random procedure based on underlying cause of death (UCOD) code or presence of certain ICD-9/10 discharge diagnosis codes. Because of this, all analyses were weighted by the inverse of sampling fractions.

III.C Medications

Medications and procedures were obtained from hospital pharmacy records and medical record review during the abstraction process. Our analysis included data on 7 medication classes: aspirin, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, lipid-lowering medications, non-aspirin anti-platelet agents, and heparin; and 4 reperfusion/revascularization procedures: coronary artery bypass grafting (CABG), thrombolytic therapy (intracoronary or intravenous streptokinase, urokinase, anistreplase, anisoylated plasminogen streptokinase activator complex [APSAC], or tissue plasminogen activator [TPA] reperfusion), and coronary angioplasty (PCI) with or without the implantation of a stent. Each medication or procedure was classified as any receipt during hospitalization or at discharge (yes or no). Because abstraction of several therapies of interest began after 1987, risk estimates for the following therapies were estimated beginning with the first study year for which complete treatment information was available for all sampled events: heparin (beginning in 1992), ACE inhibitors (1992), non-aspirin anti-platelets (1997), lipid-lowering medications (1999) and stent implantation (1999).

All-cause mortality was classified as a binary variable at 3 time points: 30 days, 90 days, and 1 year after discharge. In the ARIC Surveillance study, deaths are ascertained in two ways. First, death certificates indicating cardiovascular disease as a possible UCOD are randomly sampled, reviewed and assigned a fatal diagnosis. Hospital records are abstracted for subjects with a fatal diagnosis of definite or probable MI. Second, hospital discharge records indicating potential MI admission are randomly sampled. Death at discharge is recorded for patients who die in-hospital. For patients who are discharged alive, National Death Index searches are performed to determine vital status one year after discharge.

III.C.i Time-to-treatment

The ARIC HRA form classifies patients into 8 categories according to time from symptom onset of acute cardiac symptoms to arrival at this hospital: <1 hour, 1 – <2 hours, 2 – <4 hours, 4 – <6 hours, 6 – <12 hours, 12 – <24 hours, 1 – <3 days, and ≥3 days. Time from symptom onset to reperfusion is classified as <1 hour, 1 – <2 hours, 2 – <4 hours, 4 – <6 hours, 6 – <8 hours, and ≥8 hours. In analyses of trends in time-to-treatment (Specific AIM 1.1), trends in the proportion of patients receiving treatment by a specific timepoint were evaluated (for example, proportion receiving treatment within 2 hours of symptom onset).

III. D Covariates

III. D.i Demographics

Patient demographics in ARIC surveillance are obtained from medical record reviews. Gender (male or female), race (black or white/other), age, and health insurance (Medicare, Medicaid, prepaid health plan, HMO, other, or none) are available in the surveillance records and were be evaluated as potential effect measure modifiers or confounders as described in Section 3.5.2.

III. D. ii Risk Scores

The PREDICT score has been adapted for use with ARIC data.[184] The score ranges from 0-24. One item used in the score, serum creatinine level, is not available in ARIC surveillance data, so renal failure was omitted from the PREDICT score calculation. The metric used for calculation of the PREDICT score is shown in Appendix I. We graphically confirmed the validity of the score in this cohort by examining the linear relationship between 30-day mortality rates and calculated PREDICT score.

Exposure propensity scores can be calculated for each patient using available covariate data. 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. One key feature of PS is that if it suffices to adjust for covariates X, it also suffices to adjusted for propensity score e(X), that is, ignorability given X implies ignorability given e(x).[185]

In non-randomized studies, patients who receive a particular medication may differ from those who are not on a number of covariates which may, in turn, affect survival probability. Bias may arise when treated subjects differ from untreated subjects on one or more covariates that affect both the likelihood that they will receive the treatment and their underlying survival probability, or baseline risk.[181] Analyzing patients with respect to propensity score (PS) is a method commonly used to address this problem.[186] 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, is retained and used as the propensity score for each. After creation of the score, PS is entered as a continuous or categorical predictor in a regression model to estimate the association between the medical therapy of interest and mortality endpoints.

Candidate variables for inclusion in the propensity score were selected based on literature reviews, clinical knowledge and directed acyclic graphs. Prior research has shown that including variables in the propensity score which related to the exposure but

not to the outcome reduces effect estimate precision without reducing bias, and may even increase bias.[15,16] However, including covariates associated with the outcome but not the exposure increases the precision of the estimate without increasing bias.[17] With these considerations in mind, we selected a standard set of clinical covariates that are known to be important risk factors for all-cause mortality: age (<45, 45-<55. 55-<65, 65+), male gender, race-center 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 hospitalization, history of diabetes, STEMI diagnosis, study year (1987-1991, 1992-1996, 1997-2001, 2002-2008), prior angioplasty, and prior CABG.

III. D. iii Clinical and event Characteristics

Event characteristics, including relevant clinical history, is abstracted from medical records and included in the hospital record abstraction form. Clinical variables of interest include past history of stroke, angina (any mention of prescribed nitroglycerin for chest pain or substernal symptoms precipitated by exercise and relieved by either nitroglycerin or rest), diabetes (diagnosed before or during hospitalization, or any type of oral hypoglycemic medication or insulin used prior to or during hospitalization), or previous CABG or PCI. The Charlson comorbidity was be calculated from ICD-9 discharge diagnosis codes for use in the PREDICT score calculation.

Clinical comorbidities including prior MI, hypertension, diabetes mellitus, congestive heart failure, and stroke, and in-hospital complications, including cardiac arrest and cardiogenic shock, were documented. Event characteristics of interest included prehospital delay (<2 hours, >=2 hours; defined as the interval from onset of acute cardiac symptoms to hospital arrival), emergency medical services (EMS) transport, and length of hospital stay in days.

III. E Statistical Analyses

Several analyses in this work involve the evaluation of covariates as potential effect measure modifiers or confounders. The following Directed Acyclic Graphs (DAG) show the plausible causal relationships between each covariate of interest, based on biological plausibility and evidence from extant literature (Figure 3.1). In order to be considered a confounder, a covariate in a DAG must 1) have an arrow pointing to the exposure of interest (therapy use), 2) have an arrow pointing to the outcome of interest (mortality); and 3) not be on the causal pathway between the exposure of interest (therapy use) and the outcome of interest (mortality).[187] Because of the potential bias introduced by controlling for covariates on the causal pathway,[188] only those covariates that are not affected by therapy use should be controlled for. Thus, when we remove all arrows leading from therapy use to other covariates in the DAG (Figure 3.2), we see several unblocked backdoor paths involving demographics, risk scores, hospital characteristics, and clinical variables. Once these variables are evaluated as confounders and controlled for in the model(s), these backdoor pathways from therapy use to mortality are assumed to be blocked.

Figure 3.1. Proposed DAG showing causal relationships between therapy use, covariates, and mortality

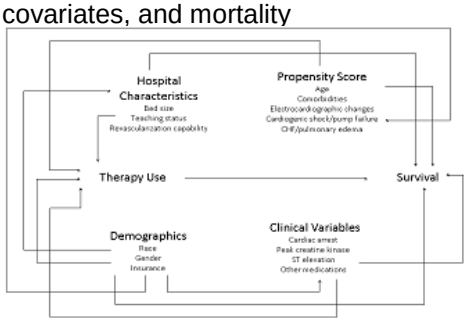
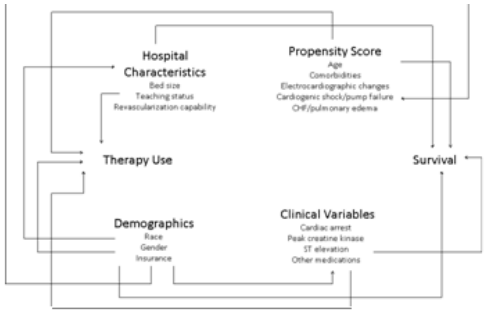


Figure 3.2. DAG with arrows from therapy use removed



III. E. i Specific Aim I

Estimate the 21-year trends of in-hospital use of 5 pharmacological interventions for acute MI including aspirin, beta blockers, calcium channel blockers, IV heparin, ace inhibitors, statins, and 3 revascularization procedures, including thrombolytic therapy, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

Each of the 11 medications and procedures were evaluated in separate regression models. Overall trends in medication and procedure use were first assessed using a simple linear model regressing medication use on treatment year and testing whether the slope of the regression line is statistically different from zero (Equation 3.5.1). However, because of the dynamic nature of medical advancements and their implementation in community practice, it was necessary to allow departure from linearity in the estimation of trends in medication use. To account for this, study year was divided into categories and build a logistic regression model with disjoint indicator variables for each study year category (Equation 3.5.2).

Equation 3.5.1. Simple linear model.

$$\ln(\text{therapy}) = \beta_0 + \beta_1(X_1)$$

where X_1 = study year (0,1,2… n)

Equation 3.5.2. Linear model with categorical indicators.

$$\ln(\text{therapy}) = \beta_0 + \beta_1(X_1) + \beta_2(X_2) + \beta_3(X_3)$$

Exposure x (years) is divided into K categories indexed by k = 1,…K. For K=4, where X_1,X_2 and X_3 are (0, 1) disjoint indicator variables for 4 categories of study year.

Equation 3.5.3. Components of the quadratic spline model to allow for departure from linearity in medication trends[5].

(a) $\ln(P(\text{therapy}) = \alpha + \beta x + \gamma_1 x^2 + \gamma_2 s^2_2 + \ldots + \gamma_k s^2_k$

where

$\alpha = \alpha^*_1$, $\beta = \beta^*_1$, $\gamma = \gamma^*_1$

$s_k = 0$ if $x <= c_k$, $x - c_k$ if $x > c_k$.

For all k>1, $\gamma_k = \gamma^*_k - \gamma^*_{k-1}$ represents the departure from linearity of the dose-response function for a 1-unit increase in k.

III. E. ii Specific Aim II

Evaluate how trends in medication and procedure use vary with important patient characteristics (age, demographics, multiple therapy, prior medical history, presenting severity) and hospital characteristics (bed size, teaching status, cardiac services capabilities).

We examined changes in study population characteristics over the study period using chi-square tests for independence with Taylor Series variance estimation to account for the complex sampling scheme. The proportion of patients receiving each medication and procedure were calculated for all study years using weighted Poisson regression. Regression estimates obtained from these models were then age-standardized to the 2000 US Census age distribution. We used multivariable loglinear regression to estimate average annual percent increases or decreases for each medical therapy overall and among STEMI and NSTEMI patients. In the figures, we present medication and procedure use for each study year; however, for ease of reporting and to promote stability in confidence interval estimates, events were grouped into intervals of 5, 6, or 7 years for table presentation. Covariates in the regression model were selected based on prior knowledge and potential for confounding in this population. To examine use of reperfusion strategies in men and women over time, we calculated RRs and 95% CIs for all study years using multivariable Poisson regression with robust variance estimation.

III. E. iii Specific Aim III

Estimate the in-hospital, 28-day and one-year mortality associated with 8 pharmacological interventions and revascularization procedures for acute MI.

Medications were first analyzed in a naïve model, where exposure will be classified as any exposure to the drug or procedure or no exposure to the drug or procedure. Logistic regression models controlling for exposure to all other medications were then used to estimate odds of 30-day and 1-year mortality for patients exposed to each drug or procedure.

III. E. IV Specific Aim IV

Evaluate how the association between survival and medical treatment varies with age, demographics, multiple therapy, prior medical history, presenting severity, clinical complications, PS/DRS and hospital characteristics

We created medical therapy-specific propensity scores using multivariable logistic regression to model 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 four sets propensity scores to account for the effect of other medications and procedures received during hospitalization. First, we created propensity scores using the standard set of clinical covariates that have been shown to be associated with survival after hospitalization, without consideration of receipt of other medications. Then, we created propensity scores with indicator variables representing all other medications and procedures in addition to this standard set of covariates. Third, we created propensity scores with the standard set of covariates and an indicator variable representing a dichotomized total number of other medical therapies received during hospitalization (<3 and >=3). Finally, we created a fourth set of propensity scores that included the standard covariate set and a variable representing the continuous total number of medications and procedures received during hospitalization. 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 propensity scores.

III. E. v Power Analyses

The null hypothesis in the proposed study is that there is no difference in odds of all-cause mortality at discharge, 28 days, or one year between patients receiving a particular therapy and those who do not. For the following power analyses, we have chosen an a priori alpha value of 0.05 to minimize the probability of committing a Type 1 error. In the proposed study, we consider Type 1 errors to be more serious than Type 2 errors. Of 61744 patients with complete HRA forms, 1619 (3%) died in hospital, 4958 (8%) died at 28 days, and 6229 (10%) died within 365 days. Using these proportions, a total sample size of total definite/probable MI patients (n=17231) and a predefined alpha level, we calculated odds ratios and the corresponding power to detect those odds ratios for varied exposure and outcome proportions.

I performed power calculations for the logistic regression components of the proposed analysis using StudySize 2.0 software (Frolunda, Sweden). One of our study aims is to characterize the proportion of definite and probable MI patients receiving particular therapies. Because the actual proportion of patients receiving each therapy is not yet known, we calculated power for 8 possible proportions of patients receiving individual MI treatment (X_1=1), based on publicly available data. Power calculations for proportions of (X_1=1) ranging from 0.05 to 0.4 in increments of 0.05 are shown for all-cause mortality at hospital discharge, 28 days after discharge, and 365 days after discharge. For this analysis, the multiple correlation of X_1 with X_2 to X_p was set to 0.4.

As shown in the tables below, our power for to detect differences in odds of mortality using the logistic regression model at treatment probability of 0.20 is excellent for ORs

above 1.4 for mortality at discharge and 1.2 for mortality at 28 days and 365 days after discharge. If the proportion of the sample receiving particular therapies is very small (0.05), our power to detect differences is inadequate for odds ratios under 2.0 for mortality at discharge and under 1.6 for mortality at 28 days and 365 days after discharge. However, we anticipate that most therapies will be used in at least 10% of definite and probable MI patients, a scenario in which we have approximately 72% power to detect ORs as small as 1.5 in the mortality at discharge group and 70-78% power to detect ORs as small as 1.3 in the 28-day and 265-day mortality groups (see tables below).

Table 3.1. Power analysis for 28-day mortality endpoint

Logistic Regression (Binary covariate). 2-sided.
Power as a function of H1: Odds Ratio and Proportion of Sample with X1 = 1.
Significance Level=0.05 H1: Prob (Event at X1=0)=0.03 Mult. Corr. of X1 with X2 to Xp=0.4
Sample Size=17231

H1: Odds Ratio	Proportion of Sample with X1 = 1							
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40
1.1	0.0599	0.0786	0.0956	0.1106	0.1236	0.1345	0.1431	0.1494
1.2	0.1047	0.1770	0.2431	0.3004	0.3480	0.3860	0.4148	0.4350
1.3	0.1806	0.3377	0.4687	0.5691	0.6427	0.6949	0.7305	0.7532
1.4	0.2856	0.5339	0.7019	0.8044	0.8650	0.9007	0.9216	0.9334
1.5	0.4127	0.7202	0.8704	0.9365	0.9658	0.9793	0.9858	0.9889
1.6	0.5489	0.8589	0.9569	0.9854	0.9942	0.9972	0.9984	0.9988
1.7	0.6786	0.9407	0.9891	0.9976	0.9993	0.9997	0.9999	0.9999
1.8	0.7887	0.9793	0.9979	0.9997	0.9999	1.0000	1.0000	1.0000

Table 3.2. Power analysis for 365-day mortality endpoint

Logistic Regression (Binary covariate). 2-sided.
Power as a function of H1: Odds Ratio and Proportion of Sample with X1 = 1.
Significance Level=0.05 H1: Prob (Event at X1=0)=0.1 Mult. Corr. of X1 with X2 to Xp=0.4
Sample Size=17231

H1: Odds Ratio	Proportion of Sample with X1 = 1							
	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40
1.1	0.0995	0.1565	0.2082	0.2533	0.2912	0.3220	0.3456	0.3624
1.2	0.2600	0.4680	0.6211	0.7252	0.7935	0.8377	0.8658	0.8827
1.3	0.5018	0.7988	0.9204	0.9664	0.9841	0.9915	0.9947	0.9962
1.4	0.7406	0.9590	0.9935	0.9988	0.9997	0.9999	1.0000	1.0000
1.5	0.8994	0.9957	0.9998	1.0000	1.0000	1.0000	1.0000	1.0000
1.6	0.9714	0.9998	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
1.7	0.9941	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
1.8	0.9991	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000

III. F Methodologic Strengths and Limitations

III.F.i Study Population

The ARIC surveillance study provides a geographically and racially diverse patient population in which to examine mortality and procedure use. The study includes validated data on hospitalized MI in four US communities spanning twenty years, during which a number of medical advancements were developed and first used in clinical practice. The hospital record abstraction form in ARIC surveillance provides a large number of important clinical variables, including laboratory values and electrocardiographic readings, which may be used to account for underlying mortality risk and probability of exposure to specific medical therapies.

Follow-up for ARIC surveillance is currently limited to one year after hospital discharge, and available outcomes are limited to mortality as reported via death certificates. However, longer-term follow-up and other outcomes of interest (stroke, future revascularization, and recurrent MI) are possible with use of the ARIC cohort data. If associations of interest in short-term (1-year) mortality are documented, we may further explore these associations in using a subset of cohort members, for whom 20 years of data on mortality, reinfarction, and adverse outcomes other than MI are available.

III.F.ii Risk Prediction

Complete data on patient-level contraindications to all medications of interest are not available in this study. However, I hope to account for variables that may influence both probability of receiving a specific therapy and risk of survival through the use of exposure propensity scores and/or disease risk scores. The PREDICT score is a validated metric that predicts mortality in ACS patients from clinical presentation data. The score has performed well in analyses of mortality in all three timepoints of interest in

this study, with C-statistics in the range of 0.76 – 0.77. It has also showed comparatively better discriminatory accuracy than another risk score commonly used in analyses of MI patients.[179]

Exposure propensity scores represent another method for accounting for differential treatment probabilities in non-randomized patients. Probabilities of receiving a particular treatment are calculated based on a number of covariates in a regression model, and matched sets or strata of subjects are constructed using results from the model. This "virtual randomization" has been shown to result in equal distribution of included covariates in treated and untreated patients.[180]

III.F.iii CHD Mortality

The outcome of interest in the present study is all-cause mortality as identified using publicly-available death records. One option when examining deaths related to hospitalization is to include only those deaths identified as CHD-related on the death certificate. Cause of death on the death certificate is determined by health department trained nosologists according to the ICD-9, and underlying cause of death (UCOD) is then assigned using the Automated Classification of Medical Entities (ACME) system. However, the use of cause of death as listed on death certificates presents limitations. In one study of the validity of the death certificate in identifying CHD deaths in ARIC surveillance, Coady, et al (2001) found that the death certificate overestimated CHD mortality by nearly 20% in the four ARIC study communities.[189] Furthermore, the false-positive rate was found to vary significantly between study communities. Finally, in order to make valid comparisons to other community-based studies on case fatality, all-cause mortality is most appropriate. Because of the limitations inherent in using CHD-specific mortality and need for comparability to other studies, all-cause mortality will be examined as the outcome of interest in these analyses.

III.F.iv Specific Aims 1 & 2

One strength of the analysis on trends in medical therapy is the use of quadratic splines to allow for departure from linearity in temporal trends. A common choice in the analysis of time trends is an arbitrary categorization of events (for example, dividing patients by study year 1987-1991, 1992-1995, etc). However, as shown by Greenland (1995), this method may present biased estimate when most subjects are exposed in a very narrow range within the categories or when exposure effects are more strongly seen at extreme ends of the exposure scale. This can lead to individuals at elevated risk being “submerged” by lower-risk members of their respective percentile categories. Quadratic splines minimize this problem by allowing for departure from linearity both within and between categories.

III.F.v Specific Aims 3 & 4

Of note is the decision to use logistic regression modeling instead of survival analysis or Cox proportional hazards models. For studies with short follow-up (up to 5 years) and low incidence of event occurrence, the two models yield similar regression coefficients.[190,191 192] Additionally, the asymptotic relative efficiency has been shown to be very close to 1 when there is a dichotomous covariate (in our study, therapy use) and identical censoring times for all subjects (in our study, 1 year after discharge). The proportional hazards assumption is an additional assumption required by the use of the Cox model, but not with the use of logistic regression. The short follow-up time, low incidence of event occurrence, and fewer model assumptions make the logistic regression modeling approach appropriate for this analysis.

The analysis of survival and therapy use in MI is strengthened by the inclusion of a number of covariates that have been shown to affect both treatment and post-discharge mortality, specifically propensity scores. Additionally, because our observations are

naturally clustered within hospitals, there is potential for underestimation of error terms when using traditional survival or regression analysis, where all observations are treated as independent. To account for this, we plan to use multilevel (mixed) models in the model building process to obtain more accurate estimates of standard errors. Mixed models contain additional terms to allow for distributional effects (or “random effects”) in addition to the fixed effects observed in traditional regression. The random effects build a probability distribution into the model to account for the hierarchical structure of the data, and to allow for variation within data clusters (hospitals).

IV. RESULTS

IV.A Manuscript 1: Temporal trends in medical therapies for ST- and Non-ST Elevation Myocardial Infarction: The Atherosclerosis Risk in Communities (ARIC) Surveillance Study

IV.A.i Introduction

A wealth of data from clinical trials and observational studies has led to major advances in medical care for hospitalized MI over the past 3 decades.[15,16,193] The availability of medical therapies for in-hospital management of MI is increasing annually,[4,27] and the use of these therapies has substantially contributed to the decreasing MI death rates over the past three decades.[12,16,23] However, the abundance of data on medical treatment for MI has done as much to set the standard of care as it has to diversify it. Evidence-based therapies and changes in guidelines typically take time to disseminate into clinical practice, and implementation of such therapies may vary by provider and geographic region.[194] Monitoring both the patterns of use of evidence-based therapies and the outcomes of treated patients is important in shaping future clinical decisions and further reducing mortality due to coronary heart disease (CHD).

Reports from large observational studies have characterized recent temporal trends and treatment patterns for MI.[8,22,25,29,195-197] Conclusions from existing reports have been limited, however, by selection, short follow-up periods, racially and/or geographically homogenous populations, and unvalidated clinical data. Furthermore, few studies have examined differences in temporal trends in the treatment of patients presenting with ST elevation myocardial infarction (STEMI) versus non-ST elevation myocardial infarction (NSTEMI), especially since this redefinition of acute MI resulted in a divergence in treatment recommendations by MI subclass beginning in 2000.[198] Clinical trials have

historically focused on STEMI patients, which may translate to wider availability of STEMI-specific treatment information and more rapid implementation of evidence-based therapies for STEMI patients than for NSTEMI patients over time. Finally, a number of studies have documented disparities in the receipt of reperfusion by gender,[199-201] but few have examined whether these disparities have improved over time.

This report characterizes temporal trends in the in-hospital treatment of STEMI and NSTEMI patients over a 21-year period in the Atherosclerosis Risk in Communities (ARIC) Study surveillance communities, a large, population-based, racially and geographically diverse study population using validated clinical data and validated MI diagnostics.

IV.A.ii Methods

The design of the community surveillance component of the Atherosclerosis Risk in Communities (ARIC) study has been described.[202] Briefly, it is a continuous retrospective surveillance study of hospitalized coronary heart disease (CHD) events with mortality follow-up designed to estimate trends in CHD incidence and mortality using standardized criteria and methods in four U.S communities: Forsyth County, North Carolina; Jackson, Mississippi; eight suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Eligible events included inpatient and out-of-hospital deaths due to CHD and hospitalized nonfatal MI 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.[203] Trained abstractors investigate hospitalizations randomly sampled from annual discharge lists obtained from each hospital serving the four ARIC communities. Events were 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 were reviewed, and relevant

clinical information was abstracted onto standardized forms. Collected data items included presenting symptoms; timing of symptom onset; history of MI, angina, and other cardiovascular conditions; in-hospital medications, diagnostics, and medical procedures; laboratory values for a number of relevant cardiac biomarkers; and up to 3 sets of twelve-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 Center were utilized to ensure reproducibility.

MI Diagnostics

A computerized algorithm using electrocardiogram readings, history of chest pain, and cardiac biomarker levels (total creatinine phosphokinase(CK), creatinine phosophokinase-myocardial band (CK-MB), lactate dehydrogenase (LDH), troponin I, and troponin T) was used to assign an MI diagnosis to sampled hospitalized events. Using this algorithm, events were classified as one of the following: 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 elevation MI using pain presentation and Minnesota-coded electrocardiogram data from the first, third, or last ECG performed during hospitalization. Multiple hospitalizations occurring within 28 days were combined and treated as one event. Any event requiring review (for example, events where the computer-derived classification of definite MI disagreed with the ICD-9-CM codes for discharge diagnosis) was independently classified by two trained reviewers. Any disagreements in diagnoses were then adjudicated by a third reviewer.

Medical therapies

Medications and procedures were obtained from hospital pharmacy records and medical record review during the abstraction process. Our analysis included data on 7 medication classes: aspirin, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, lipid-lowering medications, non-aspirin anti-platelet agents, and heparin; and 4 reperfusion/revascularization procedures: coronary artery bypass grafting (CABG), thrombolytic therapy (intracoronary or intravenous streptokinase, urokinase, anistreplase, anisoylated plasminogen streptokinase activator complex [APSAC], or tissue plasminogen activator [TPA] reperfusion), and coronary angioplasty (PCI) with or without the implantation of a stent. Each medication or procedure was classified as any receipt during hospitalization or at discharge (yes or no). Because abstraction of several therapies of interest began after 1987, trends for the following therapies were estimated beginning with the first study year for which complete treatment information was available for all sampled events: heparin (beginning in 1992), ACE inhibitors (1992), non-aspirin anti-platelets (1997), lipid-lowering medications (1999) and stent implantation (1999).

Covariates

Patient demographics were obtained from medical record reviews. Demographics of interest included gender (male or female), race (black or white/other) and age. Clinical comorbidities including prior MI, hypertension, diabetes mellitus, and stroke were collected. Event characteristics of interest included prehospital delay (<2 hours, 2-6 hours, > 6 hours; defined as the interval from onset of acute cardiac symptoms to hospital arrival), emergency medical services (EMS) transport, and length of hospital stay in days.

In order to adjust for disease severity and clinical comorbidity, we utilized a modified Predicting Risk of Death in Cardiac Disease Tool (PREDICT) score.[178] The score is a validated metric that predicts mortality in acute coronary syndrome patients from clinical presentation data, including cardiogenic shock, history of MI or cardiac procedures, age, severity of electrocardiographic changes, congestive heart failure, and Charlson Comorbidity Index. Data on renal function were not collected and therefore were omitted from our PREDICT score calculation.

Exclusion criteria

From 1987 – 2008, 32137 definite or probable MIs in subjects aged 35-74 years old were sampled in ARIC surveillance. We excluded patients whose race was not classified as black or white (n=658) and due to insufficient sample sizes, black patients who were sampled in Minnesota or Washington County, Maryland (n=493). After these exclusions, the final sample size for analysis was 30,986 definite or probable MI events.

Statistical Analyses

All estimates presented are weighted to account for the ARIC surveillance sampling scheme.[204] We examined changes in study population characteristics over the study period using chi-square tests for independence with Taylor Series variance estimation to account for the complex sampling scheme. The proportion of patients receiving each medication and procedure were calculated for all study years using weighted Poisson regression. Regression estimates obtained from these models were then age-standardized to the 2000 US Census age distribution. We used multivariable loglinear regression to estimate average annual percent increases or decreases for each medical therapy overall and among STEMI and NSTEMI patients. In the figures, we present medication and procedure use for each study year; however, for ease of reporting and to promote stability in confidence interval estimates, events were grouped into intervals of

5, 6, or 7 years for table presentation. Covariates in the regression model were selected based on prior knowledge and potential for confounding in this population. To examine use of reperfusion strategies in men and women over time, we calculated RRs and 95% CIs for all study years using multivariable Poisson regression with robust variance estimation. All models were run on the subset of definite and probable MI patients within the entire surveillance population to ensure correct calculation of standard errors. To account for the complex sampling scheme, all analyses were conducted using SAS-callable SUDAAN (release 9.2; Research Triangle Institute, Research Triangle Park, North Carolina).

IV.A.iii Results

Table 4.1.1 shows selected study population characteristics over time in 5-year intervals. From 1987 to 2008, 30,986 definite or probable MI events were sampled in the four study communities. Of these, 6106 (19.7%) were classified as STEMI, and 20302 (65.5%) were classified as NSTEMI. The proportion of patients classified as neither STEMI nor NSTEMI (14.8%) remained stable over the study period. Gender and age distribution remained relatively stable over the study period. Mean length of stay in days (95% CI) decreased substantially over the study period, from 10.1 (9.8, 10.5) days for patients in the first interval (1987-1991) to 6.4 (6.0, 6.8) days in the last interval. The prevalence of hypertension, diabetes, and stroke all increased throughout the study period, while the proportion of patients with a prior MI declined. The number of patients arriving by EMS transport increased during the study period, with 36.9% arriving by EMS in the first interval compared to 48.2% in the last interval. The proportion of patients classified as STEMI decreased from 19.6% in the first interval to 15.4% in the last interval, while the proportion of NSTEMI patients increased from 66.1% interval to 72.0% in the final interval.

Table 4.1.2 presents the proportion of patients receiving each medication and procedure of interest by year, age-standardized to the 2000 US Census population. We observed increases in the use of aspirin, beta blockers, ACE Inhibitors, lipid-lowering medications, non-aspirin anti-platelet agents, and heparin throughout the study period. Calcium channel blocker use decreased. The proportion of patients receiving thrombolytics decreased from 17% in 1987 to 0.8% in 2008. PCI use increased (15% in 1987 to 37% in 2008) while the use of CABG decreased (17% in 1987 to 7% in 2008). Data on the use of stents was first collected in 1998. Since then, the proportion of all MI patients receiving stents increased (9% in 1998 to 18% in 2008). Temporal trends for all patients and for STEMI/NSTEMI patients are illustrated for selected medications and procedures in Figure 4.1.1.

Figure 4.1.2 presents the average annual percentage change in the use of 7 medications and 4 procedures in ARIC surveillance from 1987-2008 by STEMI and NSTEMI classification, adjusted for sex, age, race*center classification, and PREDICT score. (Note: a reported percent change of 5% indicates an increase of 5% per year on average in the use of that particular medication or procedure during the study period). Similar trends were seen among STEMI and NSTEMI patients: increases (%) were noted in the use of ACE inhibitors (STEMI: 6.4, 95% CI: 5.7 to 7.2; NSTEMI: 5.5, 95% CI: 5.0 to 6.1), non-aspirin anti-platelet agents (STEMI: 5.0, 95% CI: 4.0 to 6.0; NSTEMI: 3.7, 95% CI: 2.7 to 4.7), lipid-lowering medications (STEMI: 4.5, 95% CI: 3.1 to 5.8; NSTEMI: 3.0, 95% CI: 1.9 to 4.1), beta blockers (STEMI: 2.7, 95% CI: 2.4 to 3.0; NSTEMI: 4.2, 95% CI: 3.9 to 4.4), aspirin (STEMI: 1.2, 95% CI: 1.0 to 1.3; NSTEMI: 1.9, 95% CI: 1.6 to 2.1), and heparin (STEMI: 0.8, 95% CI: 0.4 to 1.3; NSTEMI: 1.7, 95% CI: 1.3 to 2.1). Calcium channel blocker use decreased for both STEMI (-8.8%, 95% CI: -9.6 to -8.0) and NSTEMI (-5.6, 95% CI:-6.1 to -5.1) patients over the study period.

Temporal trends in the receipt of reperfusion and revascularization procedures were also similar for STEMI and NSTEMI patients. There were decreases in the use of thrombolytics (STEMI: -7.2%, 95% CI: -7.9 to -6.6; NSTEMI -9.8%, 95% CI: -10.7 to -8.8) and CABG (STEMI: -2.4%, 95% CI: -3.6 to -1.2: NSTEMI: -2.5, 95% CI: -3.3 to -1.6). PCI and stent use increased for both STEMI (PCI: 6.4; 95% CI: 5.8 to 7.0; stent: 4.5; 95% CI: 2.7 to 6.2) and NSTEMI (PCI: 5.1; 95% CI: 4.5 to 5.7; stent: 1.3; 95% CI: -0.5 to 3.2) patients.

We also examined trends in prehospital delay among STEMI and NSTEMI patients over time. The proportion of patients arriving in prespecified time intervals of <2 hours, 2-6 hours, and >6 hours by STEMI/NSTEMI classification is shown in Figure 4.1.3. A higher proportion of STEMI patients arrived within 2 hours of symptom onset than NSTEMI patients during all study years. In models adjusting for age, sex, race, and center, the proportion of patients arriving within 2 hours decreased slightly over the study period (-0.46; -0.97, 0.05). Small annual percent changes were observed for both STEMI (0.14; -0.60, 0.90) and NSTEMI (-0.33; -1.0, 0.34) patients. The percent of patients arriving within 2 hours of symptom onset was relatively stable over the study period for both STEMI and NSTEMI patients.

Finally, we examined reperfusion and revascularization rates in in male and female STEMI and NSTEMI patients. Risk ratios and 95% CIs comparing receipt of any reperfusion/revascularization strategy (PCI, PCI with stent, CABG, or thrombolytics) among men versus women for each study year are shown in Figure 4.1.4. Crude rates of reperfusion/revascularization were higher among men than among women for all study years. However, after adjustment for age, race*center, PREDICT score, and STEMI/NSTEMI classification, we did not observe significant differences in rates of reperfusion across gender strata.

IV.A.iv Discussion

To our knowledge, this is the first study to present long-term trends in-hospital treatment for both STEMI and NSTEMI patients using validated clinical data. The ARIC community surveillance study offers several advantages in the estimation of in-hospital MI treatment trends, including its large, geographically and racially diverse population, 21-years of followup, population-based sampling scheme, and detailed clinical event data and validated MI diagnostics.

We observed an increase in the use of 6 of the 7 medications of interest over the study period among STEMI and NSTEMI patients. The largest increases were in ACE inhibitors, non-aspirin anti-platelets, lipid-lowering medications, and beta-blockers. Smaller increases were noted for aspirin and heparin. These increases were significant after adjustment for age, gender, race and study center, and PREDICT score, did not differ by MI subclass, and are consistent with findings from other populations documenting increases in the use of aspirin,[8,195,196,205,206] beta-blockers,[8,68,195,196] and ACE inhibitors.[8,195,196,207] Calcium channel blockers were the only class of medications for which we observed a decrease. The magnitude of decrease was similar to that reported in other populations.[8,196] The overall results of increasing use of evidence-based pharmacological interventions for hospitalized MI are consistent with those of other studies reporting trends in increasing quality of care and better guideline adherence for acute MI patients.[145,208,209] The trends reported in this study are temporally consistent with the publication of the 1996 ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction, which recommended administration of aspirin immediately upon arrival, early administration of beta-blockers regardless of reperfusion strategy, and ACE Inhibitors for non-contraindicated patients. We also noted an increase in the use of non-aspirin anti-platelets following the 1999 update to the ACC/AHA

guidelines, which recommended Glycoprotein IIb/IIIa inhibitors for NSTEMI patients and clopidogrel as an acceptable substitute in patients contraindicated to aspirin.

A number of studies of reperfusion in MI conducted in the early 1990's reported persistent gender disparities in the receipt of PCI, CABG, and/or thrombolytics.[199-201] We compared receipt of any reperfusion strategy among men and women over the study period. Crude estimates indicated that men were more likely than women to receive reperfusion at all time points. However, after adjustment for age, race*center, PREDICT score and STEMI classification, we no longer observed significant differences in the use of any reperfusion strategy in women compared to men. These findings are consistent with those of several studies that suggest gender differences in reperfusion rates may be accounted for by other clinical variables and event characteristics.[210-212]

This study also presents trends in pharmaceutical treatments and reperfusion procedures by MI subclass. NSTEMI and STEMI were introduced as subclasses for acute MI in 2000.[213] While both STEMI and NSTEMI release markers of necrosis that reflect acute MI, a classification of STEMI indicates acute myocardial ischemia or necrosis as evidenced by electrocardiographic data. Few studies have examined long-term trends in management of NSTEMI and STEMI. Data from the National Registry of Myocardial Infarction (1990-2006) reported similar improvements in quality of care over the study period for STEMI and NSTEMI patients.[145]

Increases in PCI with stent use were noted for both STEMI and NSTEMI. The rate of PCI use increased for both STEMI and NSTEMI throughout the study period. However, PCI use increased markedly among STEMI patients after 1999, contemporaneous to the publication of the AHA 1999 Update to Guidelines for the Management of Patients with Acute Myocardial Infarction, which recommended balloon inflation for PCI within 90

minutes of hospital arrival for eligible patients. Rates of CABG declined steadily throughout the study period for both STEMI and NSTEMI patients. The use of thrombolytics increased from 1987-1990 for both STEMI and NSTEMI patients, concurrent with the publication of results from two European trials, GISSI (1986) and ISIS-2 (1988), which reported mortality reductions with thrombolytics compared to placebo.[214,215] However, the use of thrombolytics declined sharply after 1994, following the introduction of PCI and the publication of a number of trials reporting better clinical outcomes among patients treated with angioplasty compared to those treated with thrombolytics.[216]

In a 2007 analysis of medical management of 2151 STEMI and NSTEMI patients, Montalescot, et al, reported similar in-hospital and long-term prognosis among STEMI and NSTEMI patients.[144] However, NSTEMI patients underwent reperfusion less frequently and with greater time delays than STEMI patients. We noted similar disparities in reperfusion rates among NSTEMI and STEMI patients at all time points. However, significantly fewer NSTEMI patients presented within 2 hours of symptom onset, which may have affected eligibility for time-dependent reperfusion strategies such as thrombolytics. Additionally, clinical trial data suggests that early, invasive strategies for NSTEMI management may not confer any increased benefit in long-term survival compared to more selective or delayed invasive strategies.[217-219] Further monitoring of long-term outcomes in NSTEMI patients treated with early invasive strategies compared to less-invasive strategies is needed.

This study has a number of limitations. Several reports have underscored the importance of aggressive medical therapy early on in hospitalization for acute MI. One limitation of this analysis is the structure of the medication data element, which captures medications prescribed at any point during hospitalization or at discharge. We did not

have information on timing of administration, which limited our ability to make comparisons between early or delayed medication use. We were also unable to distinguish between medication use during hospitalization and at discharge.

An additional limitation of this study is the possibility of confounding by indication. It is possible that the observed increases in medication use over time are due to increasing proportions of patients eligible for each therapy, especially medications which may also be used for other medical conditions besides acute MI (e.g., hypertension, heart failure).[220] Because we do not have data on eligibility for each medication of interest, we were unable to examine the impact of patient-specific indications on temporal trends in MI therapy. However, we did utilize the PREDICT score to account for in-hospital complications and patient comorbidities, which are likely to influence treatment decisions. To assess changes in the comorbidity burden in this population, we analyzed temporal trends in mean PREDICT score, a validated score that includes a comorbidity index and clinical event data. We did not observe significant changes in mean PREDICT score over time for among STEMI or NSTEMI patients.

Finally, medication and procedure data were abstracted by chart review of sampled events from 4 US communities and may not be representative of practice patterns at all hospitals across the United States.

We found trends of increasing use of evidence-based medicine for both STEMI and NSTEMI patients over the past 22 years. Future research should examine the effect of such trends on survival after hospital discharge and the broader public health impact of increasing dissemination of information and adherence to evolving guidelines.

Table 4.1.1. Characteristics of definite and probable MI patients overall and by event year groups in the ARIC Community Surveillance Study, 1987-2008.

Variable	Overall N=30986* (%)	1987-1991† N=7524 (%)	1992-1996 N=7730 (%)	1997-2001 N=7380 (%)	2002-2008 N=8352 (%)
Age (mean, SD)	60.4 (12.0)	61.1 (10.9)	60.6 (11.7)	60.5 (11.9)	59.6 (13.7)
Male gender	20360 (65.7)	4940 (65.7)	5207(67.4)	4813 (65.2)	5400 (64.7)
Race-Center Classification					
Forsyth Black	3273 (10.6)	616 (8.2)	777 (10.0)	832 (11.3)	1047 (12.5)
Forsyth White	8889 (28.7)	2103 (28.0)	2311 (29.9)	2130 (28.9)	2345 (28.1)
Jackson Black	3805 (12.3)	621 (8.3)	752 (9.7)	1005 (13.6)	1427 (17.1)
Jackson White	3276 (10.6)	1145 (15.2)	929 (12.0)	681 (9.2)	522 (6.3)
Minnesota Whites	6320 (20.4)	1584 (21.1)	1566 (20.3)	1407 (19.1)	1762 (21.1)
Washington Whites	5422 (17.5)	1454 (19.3)	1396 (18.1)	1324 (17.9)	1248 (15.0)
Comorbidities					
Prior MI	10085 (32.7)	2784 (37.2)	2672 (34.7)	2417 (33.0)	2211 (26.5)
Hypertension	19718 (63.9)	4285 (57.3)	4617 (59.9)	4855 (66.2)	5961 (71.6)
Diabetes	7743 (34.4)	---	2034 (30.2)	2499 (34.1)	3188 (38.3)
Stroke	2873 (9.3)	583 (7.8)	796 (10.3)	741 (10.1)	753 (9.0)
PREDICT score‡ (mean)	9.5 (9.4, 9.5)	9.6 (9.5, 9.6)	9.5 (9.4, 9.5)	9.5 (9.4, 9.5)	9.3 (9.2, 9.4)
Length of stay in days (mean)	7.9 (7.8, 8.1)	10.1 (9.8, 10.5)	8.4 (8.1, 8.6)	7.0 (6.7, 7.3)	6.4 (6.0, 6.8)
Length of stay in days (median)	6.0	8.0	7.0	5.0	4.0
EMS transport	13048 (42.3)	2765 (36.9)	3171 (41.2)	3093 (42.1)	4019 (48.2)
Prehospital delay§ <2 hours	8494 (27.4)	2102 (27.9)	2176 (28.2)	2085 (28.4)	2121 (25.4)
Unknown	3632 (11.7)	912 (12.1)	857 (11.1)	821 (11.1)	1043 (12.5)
Event Classification**					
STEMI	6106 (19.7)	1474 (19.6)	1926 (24.9)	1420 (19.3)	1284 (15.4)
NSTEMI	20302 (65.5)	4970 (66.1)	4439 (57.4)	4869 (66.0)	6023 (72.1)

*Weighted number of definite or probable MI events

† Chi-square test with Taylor Series variance estimation for independence of characteristics across study years (categorical variables) or one-way ANOVA (continuous variables) significant for all variables at $p < 0.001$

‡Modified PREDICT Score did not include data on kidney function

§ Prehospital delay was defined as the interval from earliest symptom onset time to hospital arrival time

** STEMI defined as ST-elevation at any site on either the first or last ECG

Table 4.1.2. Use of medical therapy and revascularization procedures overall and by event year groups in the ARIC Community Surveillance Study, 1987-2008*.

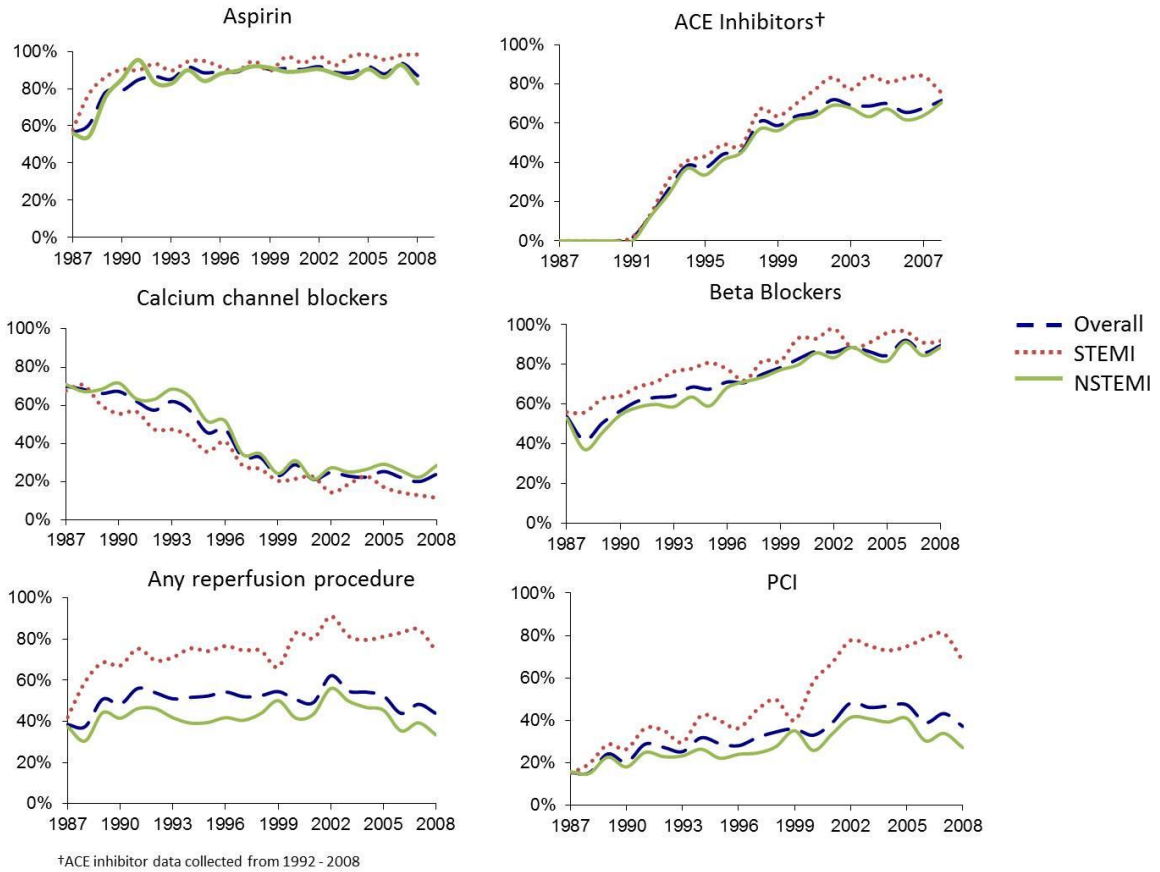
Therapy	Overall N=30986† % (SE)	1987-1991‡ N=7524 % (SE)	1992-1996 N=7730 % (SE)	1997-2001 N=7380 % (SE)	2002-2008 N=8352 % (SE)
Medication					
Aspirin	82.4 (0.22)	65.7 (0.55)	85.0 (0.41)	89.0 (0.36)	89.3 (0.34)
BB	68.0 (0.27)	45.3 (0.57)	61.3 (0.55)	75.5 (0.50)	87.9 (0.36)
CCB	44.0 (0.28)	65.3 (0.55)	54.5 (0.57)	33.0 (0.55)	24.8 (0.47)
ACEI	40.9 (0.28)	---	33.1 (0.54)	58.7 (0.57)	68.9 (0.51)
Heparin	51.6 (0.28)	---	62.4 (0.55)	71.2 (0.53)	70.3 (0.50)
Lipid-lowering medication	29.0 (0.26)	---	---	40.0 (0.57)	72.2 (0.49)
Non-aspirin anti-platelets	27.9 (0.25)	---	---	45.5 (0.58)	62.5 (0.53)
Procedures					
Thrombolytics	11.7 (0.18)	16.3 (0.43)	18.5 (0.44)	10.9 (0.36)	2.0 (0.15)
PCI	28.0 (0.25)	15.6 (0.42)	25.0 (0.49)	30.4 (0.54)	39.7 (0.54)
Stent	14.4 (0.20)	---	---	19.6 (0.46)	35.9 (0.53)
CABG	14.3 (0.20)	15.6 (0.42)	18.1 (0.44)	14.5 (0.41)	9.5 (0.32)

* Medication information for ACEI, Heparin, Lipid-lowering drugs, non-aspirin anti-platelets, and stents not collected during years indicated by dashed lines (---)

† Weighted number of definite or probable MI events

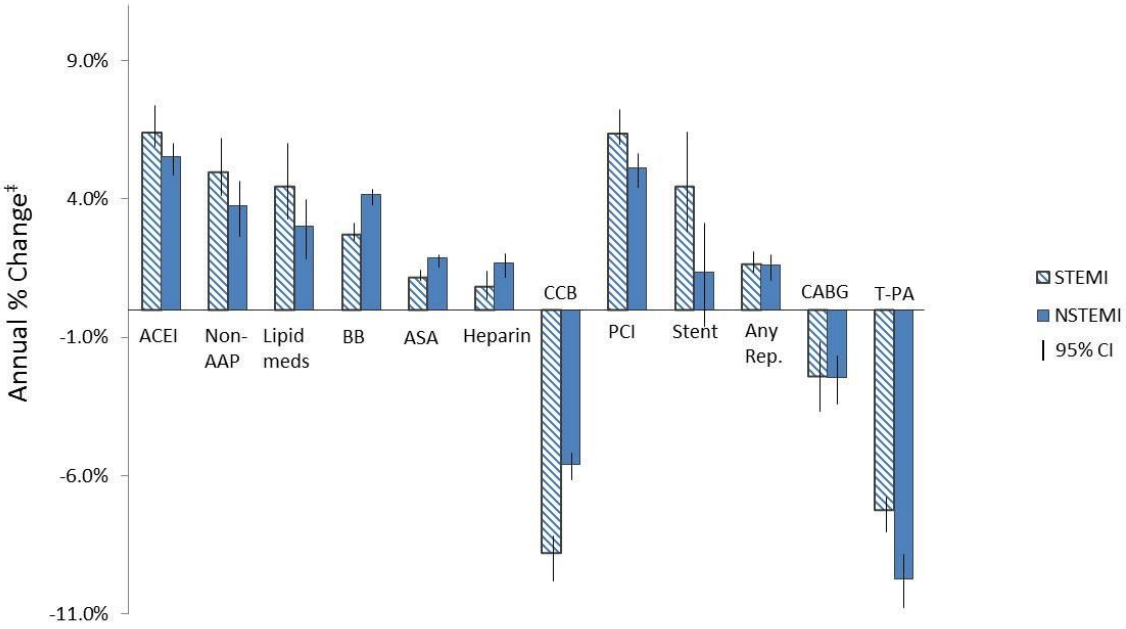
‡ Chi-square test for independence with Taylor Series variance estimation significant for all variables at p <0.001

Figure 4.1.1. Medication and procedure use by year in STEMI & NSTEMI patients in ARIC Community Surveillance: 1987 - 2008.



†ACE inhibitor data collected from 1992 - 2008

Figure 4.1.2. Average annual % change in medical therapy and reperfusion procedure* use in STEMI and NSTEMI patients in ARIC Community Surveillance: 1987- 2008†.



*Abbreviations: ACEI=ACE Inhibitors; Non-AAP=non-aspirin anti-platelets; BB=Beta Blockers; ASA=aspirin; CCB=calcium-channel blockers; PCI=Percutaneous Coronary intervention; Any rep= Any reperfusion (CABG, PCI, Stent, T-PA); CABG = Coronary artery bypass graft; t-PA = tissue plasminogen activator

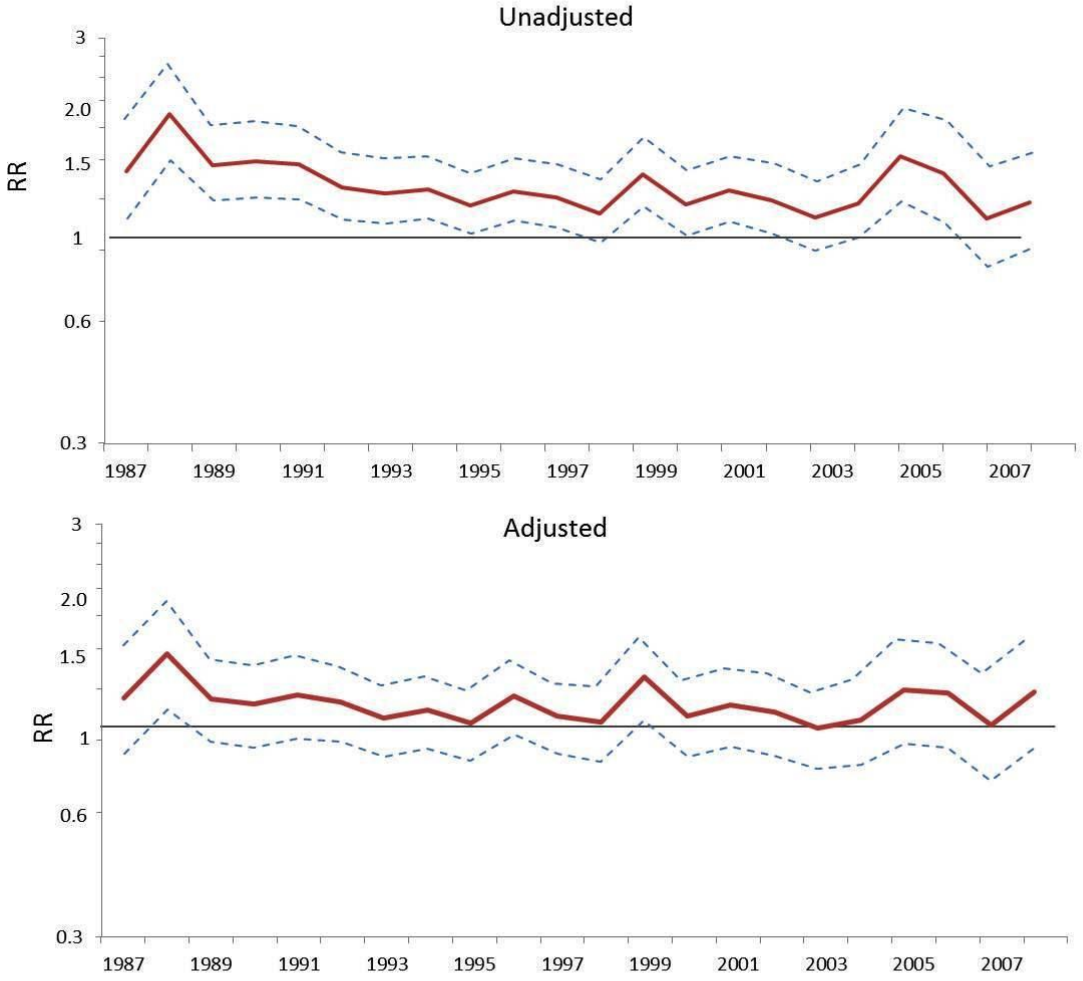
† Medical therapy data available for only part of the study period for ACEI, lipid meds, Heparin, Non-AAP, and stents

‡ Loglinear regression models adjusted for sex, race, center, age, and log-transformed PREDICT Score

Figure 4.1.3. Prehospital delay time* in STEMI and NSTEMI patients: The ARIC Community Surveillance Study: 1987- 2008.

* Prehospital delay time defined as the interval from onset of acute cardiac symptoms to arrival at the hospital

Figure 4.1.4. Adjusted and unadjusted temporal trends in risk ratios comparing receipt of any reperfusion* strategy in men versus women: The ARIC Community Surveillance Study: 1987-2008.



*Eligible reperfusion strategies included IV-tPA, PCI with or without stents, and CABG
† Weighted loglinear regression adjusting for age, race, center, PREDICT score, and STEMI classification

IV.B Manuscript 2: Medication and reperfusion therapy and survival in a community-based setting of hospitalized myocardial infarction: The Atherosclerosis Risk in Communities Surveillance Study

IV. B. i Introduction

Acute myocardial infarction (MI) is the most common direct cause of mortality due to coronary heart disease (CHD) and approximately 16% of patients who experience an MI will die within one year of hospitalization.[10] Death rates attributable to CHD have declined since the 1960s,[13,14] with nearly half of the decrease in CHD mortality attributable to medical advancements.[12] There is a rich literature of clinical trial data on medical therapies for MI and mortality. However, clinical trials are often conducted in highly-selected patient populations and may not represent what is observed in clinical practice.[169-172]

Observational studies can provide a valuable perspective into the association between medical therapy and mortality after hospital discharge as observed in community-based, hospitalized settings. However, because treatment groups in observational studies are not randomly assigned, analyses of observational data have been limited by inability to account for bias introduced by differences in underlying mortality risk between treated and untreated patients.[3] A number of methods have been proposed to address this limitation, including propensity scores (PS), which utilize a set of covariates to determine probability of treatment and result in a pseudo-randomization of subjects into exposure groups.[221] However, few studies using PS to adjust for confounding have examined modeling strategies to account for the use of multiple therapies during a single hospitalized event. In this study, we examined the association between 30-day, 90-day, and 365-day mortality and receipt of 11 medical therapies commonly used for treatment of hospitalized MI in a population-based sample of the Atherosclerosis Risk in Communities (ARIC) Study surveillance communities. We used

five unique propensity score strategies to account for the non-randomized study design and the effect of multiple medical therapies on all-cause mortality after hospitalization in a large, community-based population of validated myocardial infarction events sampled over a period of 22 years.

IV. B. ii Methods

The design of the community surveillance component of the Atherosclerosis Risk in Communities (ARIC) study has been described.[202] Briefly, it is a continuous retrospective surveillance study of hospitalized coronary heart disease (CHD) events with mortality follow-up designed to estimate trends in CHD incidence and mortality using standardized criteria and methods in four U.S communities: Forsyth County, North Carolina; Jackson, Mississippi; eight suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Eligible events included inpatient and out-of-hospital deaths due to CHD and hospitalized nonfatal MI 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.[203] Trained abstractors investigate hospitalizations randomly sampled from annual discharge lists obtained from each hospital serving the four ARIC communities. Events were 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 were reviewed, and relevant clinical information was abstracted onto standardized forms. Collected data items included presenting symptoms; timing of symptom onset; history of MI, angina, and other cardiovascular conditions; in-hospital medications, diagnostics, and medical procedures; laboratory values for a number of relevant cardiac biomarkers; and up to 3 sets of twelve-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 Center were utilized to ensure reproducibility.

MI Diagnostics

A computerized algorithm using evidence from electrocardiograms, history of chest pain, and cardiac biomarker levels (total creatinine phosphokinase(CK), creatinine phosophokinase-myocardial band (CK-MB), lactate dehydrogenase (LDH), troponin I, and troponin T) was used to assign an MI diagnosis to sampled hospitalized events. Using this algorithm, events were classified as one of the following: 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 elevation MI using pain presentation and Minnesota-coded electrocardiogram data from the first, third, or last ECG performed during hospitalization. Multiple hospitalizations occurring within 28 days were combined and treated as one event. Selected events requiring review (for example, events classified by computer as definite MI but without an ICD-10-CM 410 discharge diagnosis code) were independently classified by two trained reviewers. Any disagreements in diagnoses were then adjudicated by a third reviewer.

Medical therapies

Medications and procedures were obtained from hospital pharmacy records and medical record review during the abstraction process. Our analysis included data on 7 medication classes: aspirin, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, lipid-lowering medications, non-aspirin anti-platelet agents, and heparin; and 4 reperfusion/revascularization procedures: coronary artery bypass grafting (CABG), thrombolytic therapy (intracoronary or intravenous streptokinase, urokinase, anistreplase, anisoylated plasminogen streptokinase activator

complex [APSAC], or tissue plasminogen activator [TPA] reperfusion), and coronary angioplasty (PCI) with or without the implantation of a stent. Each medication or procedure was classified as any receipt during hospitalization or at discharge (yes or no). Because data on several therapies of interest were collected after 1987, risk estimates for the following therapies were estimated beginning with the first study year for which complete treatment information was available for all sampled events: heparin (beginning in 1992), ACE inhibitors (1992), non-aspirin anti-platelets (1997), lipid-lowering medications (1999) and stent implantation (1999).

All-cause mortality

We analyzed three outcomes of interest: 30-day, 90-day, 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, 60, and 90-day classifications represent the intervals from hospital admission date until date of death.

Covariates

Patient demographics were obtained from medical record reviews. Demographics of interest included gender (male or female), race (black or white/other), center (Minnesota, Washington County, Forsyth County, or Jackson) and age. Clinical comorbidities including prior MI, hypertension, diabetes mellitus, congestive heart failure, and stroke, and in-hospital complications, including cardiac arrest and cardiogenic shock, were documented. Event characteristics of interest included prehospital delay (<2 hours, >=2 hours; defined as the interval from onset of acute cardiac symptoms to hospital arrival), emergency medical services (EMS) transport, and length of hospital stay in days.

Exclusion criteria

From 1987 – 2008, 32137 definite or probable MIs in subjects aged 35-74 years old occurred 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 Scores

In non-randomized studies, patients who receive a particular treatment may differ on a number of covariates from those who do not receive these treatments. These differences may, in turn, affect survival probability. Bias may arise when treated subjects differ from untreated subjects on one or more covariates that affect both the likelihood that they will receive the treatment and their underlying survival probability, or baseline risk.[177] Analyzing patients with respect to propensity score (PS) is a method commonly used to address this problem.[180] 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 $e(X) = \text{prob}(Z = 1|X)$, 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, is retained and used as the propensity score for each. After creation of the score, PS is entered as a continuous or categorical predictor in a regression model to estimate the association between the medical therapy of interest and mortality endpoints.

Variable selection

Candidate variables for inclusion in the propensity score were selected based on literature reviews, clinical knowledge and directed acyclic graphs. Prior research has shown that including variables in the propensity score which related to the exposure but not to the outcome reduces effect estimate precision without reducing bias, and may even increase bias.[222,223] However, including covariates associated with the outcome but not the exposure increases the precision of the estimate without increasing bias.[224] With these considerations in mind, we selected a standard set of clinical covariates that are known to be important risk factors for all-cause mortality: age (<45, 45-<55. 55-<65, 65+), male gender, race-center 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 hospitalization, history of diabetes, STEMI diagnosis, study year (1987-1991, 1992-1996, 1997-2001, 2002-2008), prior angioplasty, and prior CABG.

We created medical therapy-specific propensity scores using multivariable logistic regression to model 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 four sets propensity scores to account for the effect of other medications and procedures received during hospitalization. First, we created propensity scores using the standard set of clinical covariates that have been shown to be associated with survival after hospitalization, without consideration of receipt of other medications. Then, we created propensity scores with indicator variables representing all other medications and procedures in addition to this standard set of covariates. Third, we created propensity scores with the standard set of covariates and an indicator variable representing a dichotomized total number of other medical therapies received

during hospitalization (<3 and >=3). Finally, we created a fourth set of propensity scores that included the standard covariate set and a variable representing the continuous total number of medications and procedures received during hospitalization. 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 propensity scores (data not shown).

Statistical Analyses

All estimates presented are weighted to account for the ARIC surveillance sampling scheme.[204] We used weighted multivariable loglinear regression to estimate risk ratios for the association between receipt of each medical therapy and 30-, 90-, and 365- day all-cause mortality. All models were run on the subset of definite and probable MI patients within the entire surveillance population to ensure correct calculation of standard errors. To account for the complex sampling scheme, all analyses were conducted using SAS-callable SUDAAN (release 9.2; Research Triangle Institute, Research Triangle Park, North Carolina).

We excluded all observations in the non-overlap regions of the propensity score distributions of the treated and untreated patients to ensure positivity.[225] After this exclusion, we trimmed 5% of the observations at each tail of the propensity distribution to eliminate potential bias introduced by modeling the outcome of interest in subjects who were treated contrary to prediction.[186] Finally, we examined ratio estimates for each medical therapy with propensity score modeled as either a continuous predictor or a categorical predictor, with PS included as 4 indicator variables representing quintiles of

the respective PS distributions for each medical therapy.[226] Because estimates were similar, we present results obtained from models with quintiles of PS as predictors.

IV. B. iii Results

Table 4.2.1 shows selected characteristics for 30,986 subjects with MI and by strata of 3 outcomes of interest: all-cause mortality within 30 days, 90 days, and 365 days of discharge. The unadjusted risk of death within 30 days of hospitalization for definite or probable MI was 7.5%; within 90 days, 8.6%; and within 365 days, 10.0%. Compared to the entire population of hospitalized MI patients, those who died within 30 days of hospitalization were older, less likely to be male, black, have a history of stroke, have diabetes, arrive by EMS, and be classified as NSTEMI. Similar patterns were observed in patients who died within 90 days of hospitalization and those who died within 365 days of hospitalization. Patients who died within 30, 90, or 365 days of hospitalization were less likely to have a prehospital delay time of less than 2 hours. Of all deaths that occurred within 30 days of hospitalization, 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 4.2.1 shows the distribution of total medications per hospitalization by study year category. In this figure, events were grouped into intervals of 5, 6, or 7 years to promote stability in confidence interval estimates. The mean total number of medications per hospitalization increased from 1.77 (95% CI =1.73, 1.81) in the first study year interval to 4.76 (95% CI = 4.69, 4.83) in the fourth interval. Over time, the normalized distribution of total number of medications per hospitalization shifted to the right,

indicating a higher number of medications per hospitalization in recent years compared to earlier years. Additionally, the normalized distribution of number of medications per event appears to grow wider over time, indicating increasing variability in the number of medications per hospitalization within a given study year category.

Table 4.2.2 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 hospitalization in patients who received each medical therapy. Aspirin was the most commonly used medication throughout the study period (82.4; 81.6, 83.2) followed by beta blockers (68.0; 67.1, 68.9), heparin (68.0; 66.9, 69.1), and lipid-lowering medications (67.3; 65.8, 68.8). Angioplasty was the most commonly used procedure (28.0; 27.3, 28.7), with over half of angioplasty patients receiving a stent (31.3; 30.1, 32.5). Crude mortality risks were lower for patients receiving all medications or procedure of interest than in the overall study population.

Table 4.2.3 presents risk ratios estimating the association between receipt of each medical therapy and 30-day all-cause mortality by analytic strategy. The unadjusted estimates shown in the first column (Model A. Unadjusted) indicate positive survival benefits associated with each medication and procedure. The second column (Model B. PS Only) shows results from a model including quintile indicators for a propensity score derived from regression of medical therapy receipt on a set of standard clinical covariates. After inclusion of the PS, the crude survival effects were attenuated for all therapies except for IV-tPA and stent use. The third column (Model C. PS + all other medical therapies) shows effect estimates for each therapy in a model including a PS score derived from the same set of standard clinical covariates in Model B, with the addition of indicator variables for all other medical therapies of interest. After inclusion of other therapies, effect estimates (RR;[95% CI]) were substantially attenuated for aspirin

(0.66; [0.58, 0.76] to 0.91 [0.80 to 1.03) and moderately attenuated for non-aspirin anti-platelets (0.74; [0.59, 0.92] to 0.92 [0.72 to 1.18]), IVTPA (0.50; [0.41, 0.62] to 0.65 [0.52 to 0.80]), stents (0.53 [0.40, 0.69] to 0.68 [0.49, 0.94]). Effect estimates remained stable for beta-blockers, calcium-channel blockers, lipid lowering medications, heparin, ACE Inhibitors, CABG and Angioplasty. The fourth column (Model D. PS + Number of other therapies [categorical]) shows results from a model including PS created from the standard set of covariates plus a variable representing dichotomized number of total medications per hospitalized event (<3, ≥3). Estimates from this model were similar to those from Model C, with the exception of stents (0.51 [0.42,0.63]) and IV-TPA (0.56 [0.41, 0.75]), both of which showed increased mortality benefit in Model D compared to Model C. Finally, the fifth column shows risk ratios from a model controlling for a PS created from a model of the standard set of covariates plus the continuous number of total medical therapies per hospitalization. Effect estimates from this model were moderately attenuated for all medical therapies except for angioplasty and IVTPA, which were comparable to the estimates obtained from Model D.

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.

IV. B. iv Discussion

We observed negative associations between medication use and all-cause mortality at 30, 90 and 365 days after hospitalized myocardial infarction for beta-blockers, calcium channel blockers, aspirin, lipid-lowering medications, non-aspirin anti-platelets, ACE-Inhibitors after adjustment for propensity scores created from a standard set of clinical

covariates. With the exception of non-aspirin anti-platelets, these associations were attenuated but remained significant after adding indicators for all other medical therapies to the PS regression model and after adding the continuous total number of medical therapies received to the model. With the exception of aspirin, none of the medications of interest showed a significant survival benefit when controlling for total number of medications. 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 beta-blockers,[53,54] aspirin,[39,43 41] calcium channel blockers,[64-67] ACEI Inhibitors,[80,81] heparin,[78,79] lipid-lowering medications.[85-87] As has been observed in number of clinical trials, the mortality benefit of non-aspirin anti-platelets was attenuated substantially after accounting for the use of other medications.[46,48]

Negative associations between receipt of in-hospital procedures and 30-day mortality were observed with the inclusion of PS from a standard set of clinical covariates. These associations remained relatively stable for all four procedure groups after inclusion of variables representing number and type of other medical therapies, and similar patterns were observed for 90-day and 365-day mortality endpoints. These benefits are similar to those reported in clinical trials of PCI,[110-112] PCI with stent,[110,118] IVTPA,[39,97-99] and CABG.[126-128]

This study is unique in its analysis of survival 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 randomized clinical trials, widely considered the gold standard for causal inference in the study of treatment effects.[167,168] However, results from RCTs are not always generalizable to heterogenuous populations, and are seldom entirely consistent with results from other clinical trials. Clinical trials

have stringent inclusion and exclusion criteria, and evidence from several studies indicates that clinical trial populations may not represent how MI patients are treated in routine clinical practice.[169-171] In an analysis of 36 topics with conflicting results from over 200 trials in cardiology and gastroenterology, Horwitz, et al (1987) documented multiple contradictory results in RCTs of cardiovascular treatment and survival. Investigators concluded that inconsistency in RCT results stems from differences in the clinical setting and therapeutic evaluation, including study group selection, baseline variable differences, and management of intermediate outcomes.[172] In the current study, we utilized rigorous methodology and careful covariate selection to minimize bias typically found in observational analyses.

As the total number of medications administered or prescribed during each hospitalized event increases over time, so does the importance of accounting for the effects of other medications and procedures when analyzing the survival benefit of a particular therapy. There are few examples in the scientific literature of PS strategies to account for the use of multiple therapies during a single hospitalized event. To address this issue, we created four sets of propensity scores including the number and type of other medical therapies administered during hospitalization. Results from these models suggest mortality benefits at 30-, 60-, and 90-days for beta-blockers, aspirin, lipid-lowering medications and ACE Inhibitors 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 propensity score were included in a standard loglinear regression model.

The ARIC community surveillance study offers a number of advantages in the study of medical therapy for acute MI and associated survival. The study population is a large, racially and geographically diverse community-based sample with validated myocardial infarction diagnostics. Because the ARIC study monitors hospitalized 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, because survival after myocardial infarction depends on a mix of factors, it is important to account for the key risk factors that determine survival after MI hospitalization. The ARIC surveillance study collects a large number of clinical covariates that have been shown to affect post-hospitalization mortality, including presence of comorbidities, procedure history, in-hospital complications, and STEMI/NSTEMI classification. This allowed us to account for the presence of potentially important confounders, an integral component to observational analyses of medication use and survival.

Because mortality followup is limited to one year after hospital discharge, we were unable to examine the long-term benefits of medical therapies prescribed and administered during the course of hospitalization. It is possible that benefits conferred by the therapies in our analysis become more or less pronounced with time. However, we did observe general stability in estimates between various timepoints within the one year mortality followup period of our study, so it is unlikely that there would be sudden divergence from the magnitude and/or direction of the observed benefits beginning at one year after hospitalization.

Prior studies have shown less-than-optimal adherence in patients on CHD medication regimens.[227-231] One study of statin therapy in an elderly population

documented a decline of nearly 50% in adherence after just 6 months of beginning the medication regimen.[232] We were not able to determine patterns of medication use beyond discharge, and it is likely that each group of subjects identified as taking a particular medication includes a subset of individuals who did not fill prescriptions or were less than 100% adherent to prescribed medication regimens after discharge. However, as data from clinical trials and other observational studies have documented a survival benefit associated with the use of each medical therapy of interest in this analysis, including these patients would presumably reduce the observed effect of the medical therapy analyzed.

Because the ARIC community surveillance study is observational in nature, assignment of patients to medical therapies of interest is not randomized. While we tried to account for major known confounders through the use of propensity scores, it is still possible that unmeasured confounders 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 current study protocol.

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

Table 4.2.1. Characteristics of definite and probable MI patients overall and by primary outcomes of interest in the ARIC Community Surveillance Study, 1987-2008.

Covariate	All Patients N=30986* % (SE)	Death within 30 Days† N=2337 (7.5%)	Death within 90 Days N=2669 (8.6%)	Death within 365 Days N=3106 (10.0%)
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-Center 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 hours	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)
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 hospitalized event

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

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

Table 4.2.2. Unadjusted risk of 30, 90, and 365-day mortality* and receipt of medications and procedures†: The ARIC Community Surveillance Study, 1987-2008.

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

* All-cause mortality within 30, 90 OR 365 days of the hospital arrival date
†Medication or procedure use at any point during hospitalization or medication prescription at discharge

Table 4.2.3. Risk ratios for medical therapy use* and 30-day mortality† among hospitalized 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**)		Model E. PS: standard covariates + number of other therapies (continuous)	
Therapy	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Medication										
Beta blockers	0.30	0.26, 0.34	0.67	0.58, 0.76	0.71	0.62, 0.81	0.78	0.68, 0.89	0.89	0.75, 1.06
Calcium channel blockers	0.74	0.66, 0.84	0.80	0.70, 0.92	0.85	0.74, 0.98	0.77	0.66, 0.90	0.92	0.79, 1.08
Aspirin	0.21	0.19, 0.24	0.66	0.58, 0.76	0.68	0.59, 0.78	0.65	0.57, 0.75	0.79	0.66, 0.95
Lipid-lowering medications	0.22	0.17, 0.27	0.51	0.40, 0.65	0.57	0.44, 0.73	0.71	0.53, 0.96	0.82	0.60, 1.13
Non-aspirin anti-platelets	0.32	0.27, 0.39	0.74	0.59, 0.92	0.92	0.72, 1.18	0.91	0.70, 1.18	1.18	0.90, 1.54
Heparin	0.59	0.51, 0.	0.86	0.73, 1.01	0.92	0.79, 1.07	0.96	0.81, 1.14	1.18	0.96, 1.44
ACE Inhibitors	0.53	0.45, 0.61	0.66	0.56, 0.78	0.70	0.59, 0.82	0.71	0.60, 0.84	0.87	0.71, 1.06
Procedure										
CABG	0.47	0.40, 0.56	0.60	0.50, 0.72	0.53	0.43, 0.66	0.64	0.53, 0.76	0.73	0.61, 0.88
Angioplasty	0.27	0.23, 0.31	0.45	0.38, 0.54	0.48	0.39, 0.59	0.51	0.43, 0.61	0.61	0.51, 0.74
IVTPA	0.58	0.48, 0.69	0.50	0.41, 0.62	0.65	0.52, 0.80	0.51	0.42, 0.63	0.57	0.46, 0.71
Stent	0.88	0.69, 1.13	0.53	0.40, 0.69	0.68	0.49, 0.94	0.56	0.41, 0.75	0.67	0.49, 0.92

* Medication or procedure use at any point during hospitalization or medication prescription at discharge
† All-cause mortality within 90 days of the hospital arrival date
‡ 5% of full propensity score range was trimmed from maximum values among untreated patients and minimum values among treated patients after elimination of non-overlapping scores
§ Indicator variables representing 4 highest quintiles of propensity score values calculated separately for treated and untreated patients after eliminating non-overlapping scores and trimming
** Categories of medication number were <3 and 3+

Table 4.2.4. Risk ratios for medical therapy use* and 90-day mortality† among hospitalized 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**)		Model E. PS: standard covariates + number of other therapies (continuous)	
Therapy	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Medication										
Beta blockers	0.32	0.28, 0.36	0.70	0.62, 0.80	0.75	0.66, 0.85	0.80	0.71, 0.91	0.90	0.76, 1.05
Calcium channel blockers	0.81	0.72, 0.91	0.86	0.75, 0.99	0.92	0.80, 1.05	0.83	0.72, 0.97	0.98	0.85, 1.14
Aspirin	0.23	0.20, 0.25	0.68	0.60, 0.77	0.71	0.63, 0.81	0.68	0.60 ,0.77	0.82	0.68, 0.98
Lipid-lowering medications	0.25	0.20, 0.31	0.57	0.44, 0.73	0.63	0.48, 0.82	0.73	0.55, 0.98	0.80	0.59, 1.08
Non-aspirin anti-platelets	0.34	0.28, 0.40	0.74	0.60, 0.92	0.90	0.71, 1.14	0.87	0.67, 1.14	1.04	0.78, 1.38
Heparin	0.61	0.53, 0.71	0.89	0.76, 1.03	0.94	0.81, 1.10	0.97	0.83, 1.14	1.15	0.95, 1.40
ACE Inhibitors	0.58	0.50, 0.67	0.69	0.59, 0.81	0.73	0.63, 0.86	0.74	0.63, 0.87	0.88	0.73,1.06
Procedure										
CABG	0.50	0.42, 0.60	0.64	0.54, 0.77	0.59	0.48, 0.74	0.67	0.56, 0.81	0.77	0.64, 0.93
Angioplasty	0.26	0.22, 0.30	0.44	0.37, 0.52	0.46	0.38, 0.56	0.49	0.41, 0.58	0.57	0.47, 0.68
IVTPA	0.55	0.46, 0.65	0.50	0.41, 0.60	0.65	0.53, 0.79	0.52	0.42, 0.63	0.46	0.56 0.69
Stent	0.26	0.21, 0.34	0.50	0.38, 0.65	0.60	0.44, 0.83	0.51	0.39, 0.68	0.59	0.44, 0.80

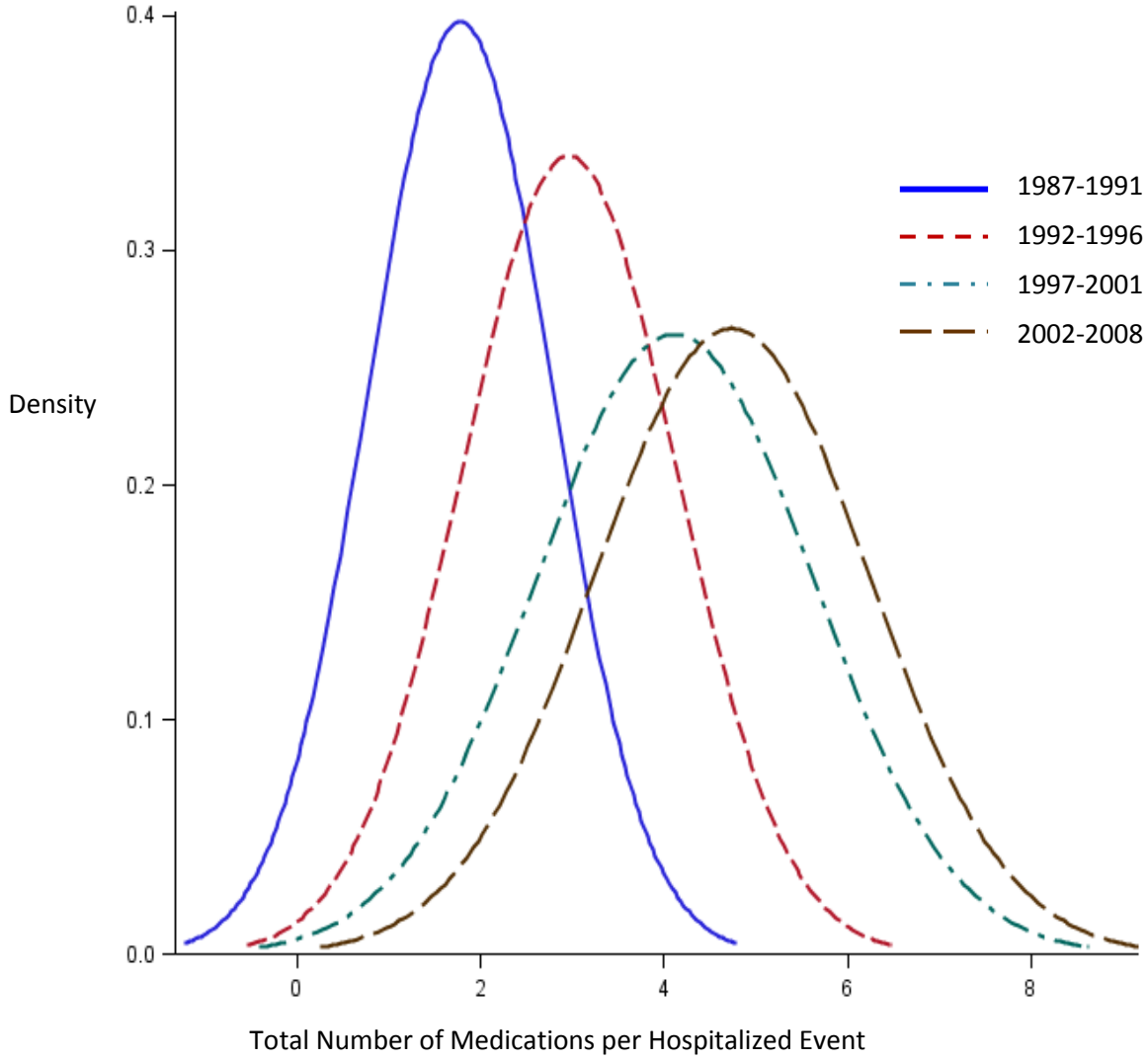
* Medication or procedure use at any point during hospitalization or medication prescription at discharge
† All-cause mortality within 90 days of the hospital arrival date
‡ 5% of full propensity score range was trimmed from maximum values among untreated patients and minimum values among treated patients after elimination of non-overlapping scores
§ Indicator variables representing 4 highest quintiles of propensity score values calculated separately for treated and untreated patients after eliminating non-overlapping scores and trimming
** Categories of medication number were <3 and 3+

Table 4.2.5. Risk ratios for medical therapy use* and 365-day mortality† among hospitalized 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**)		Model E. PS: standard covariates + number of other therapies (continuous)	
Therapy	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Medication										
Beta blockers	0.34	0.30, 0.38	0.69	0.61, 0.77	0.73	0.64, 0.82	0.79	0.69, 0.89	0.91	0.78, 1.07
Calcium channel blockers	0.80	0.72, 0.90	0.86	0.76, 0.98	0.91	0.80, 1.03	0.84	0.73, 0.96	0.98	0.85, 1.13
Aspirin	0.24	0.22, 0.27	0.65	0.58, 0.74	0.70	0.62, 0.79	0.67	0.59, 0.76	0.82	0.69, 0.97
Lipid-lowering medications	0.31	0.25, 0.37	0.61	0.49, 0.76	0.69	0.54, 0.87	0.76	0.58, 1.00	0.83	0.63, 1.09
Non-aspirin anti-platelets	0.37	0.31, 0.43	0.76	0.62, 0.93	0.94	0.76, 1.17	0.92	0.72, 1.17	1.08	0.83, 1.40
Heparin	0.61	0.54, 0.70	0.89	0.77, 1.02	0.94	0.82, 1.09	0.99	0.85, 1.15	1.17	0.98, 1.39
ACE Inhibitors	0.66	0.58, 0.76	0.73	0.62, 0.85	0.76	0.65, 0.88	0.77	0.66, 0.89	0.94	0.78, 1.12
Procedure										
CABG	0.48	0.41, 0.57	0.62	0.52, 0.74	0.59	0.48, 0.72	0.65	0.55, 0.77	0.75	0.63, 0.90
Angioplasty	0.26	0.23, 0.30	0.45	0.39, 0.53	0.49	0.41, 0.59	0.50	0.43, 0.59	0.59	0.50, 0.70
IVTPA	0.52	0.44, 0.62	0.49	0.41, 0.60	0.63	0.52, 0.77	0.51	0.42, 0.62	0.56	0.46, 0.68
Stent	0.28	0.23, 0.35	0.51	0.41, 0.65	0.63	0.48 0.83	0.56	0.44, 0.71	0.66	0.51, 0.86

* Medication or procedure use at any point during hospitalization or medication prescription at discharge
† All-cause mortality within 365 days of the hospital arrival date
‡ 5% of full propensity score range was trimmed from maximum values among untreated patients and minimum values among treated patients after elimination of non-overlapping scores
§ Indicator variables representing 4 highest quintiles of propensity score values calculated separately for treated and untreated patients after eliminating non-overlapping scores and trimming
**Categories of medication number were <3 and 3+

Figure 4.2.1. Normalized density plot of total medications per hospitalization for definite/probable MI by study year category: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).



V. CONCLUSIONS

V. A. Overall study aims and findings

A wealth of research over the past decades has contributed to better medical care and increased likelihood of survival for hospitalized MI patients. Numerous clinical trials and observational studies have expanded our knowledge of the most safe and efficacious treatments for MI; however, such data is useless if it is not implemented in the clinical care of MI patients. Overall, the proposed aims of this study, to characterize changing practice patterns for STEMI and NSTEMI in a community-based setting over the past two decades and associated survival benefits, were met.

This work documents the changing landscape of practice patterns for hospitalized MI in a representative, population-based sample over 22 years. We observed an increase in the use of 6 of the 7 medications and 3 of the 4 procedures of interest over the study period among STEMI and NSTEMI patients. The overall study results of increasing use of evidence-based pharmacological interventions for hospitalized MI are consistent with those of other studies reporting trends in increasing quality of care and better guideline adherence for acute MI patients.[145,208,209] We report trends that are temporally consistent with the publication of a number of major clinical trials and guideline updates, including the 1996 ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction, which recommended administration of aspirin immediately upon arrival, early administration of beta-blockers regardless of reperfusion strategy, and ACE Inhibitors for non-contraindicated patients. We also noted an increase in the use of non-aspirin anti-platelets following the 1999 update to the ACC/AHA guidelines, which recommended

Glycoprotein IIb/IIIa inhibitors for NSTEMI patients and clopidogrel as an acceptable substitute in patients contraindicated to aspirin. However, PCI use increased markedly among STEMI patients after 1999, contemporaneous to the publication of the AHA 1999 Update to Guidelines for the Management of Patients with Acute Myocardial Infarction, which recommended balloon inflation for PCI within 90 minutes of hospital arrival for eligible patients. These changes are evidentiary of information dissemination in the community of providers who treat MI, and rapid changes in clinical practice in response to new scientific discoveries are encouraging for policymakers, scientists, and providers with the goal of improving medical care for acute MI.

The scientific literature contains numerous examples of randomized trial results that have not been replicated in clinical practice. We analyzed the association between 11 medications and procedures that have shown to be beneficial in clinical trial populations and short-term mortality in a population-based sample of hospitalized MI. We documented substantial benefits associated with the use of beta-blockers, aspirin, lipid-lowering medications, ACE Inhibitors, CABG, angioplasty, stents, and IV-TPA for 30-, 90-, and 365-day all-cause mortality. These findings persisted when including indicators for number and type of other medications in the propensity score creation model. Few studies have examined such a large number of medical therapies for MI and associated survival. A 2011 study of 61 238 hospitalized STEMI patients in Sweden reported increases in the use of evidence based therapies over a 12-year study period and corresponding decreases in the rate of in-hospital complications and mortality.[233] However, as the authors note, this study was observational in nature, and investigators did not attempt to analyze the direct association between medical therapy use and mortality. A similar study assessed trends in long-term mortality and medication use in 10352 patients in the UK. While the authors reported decreasing case-fatality and

increasing prescription of lipid-lowering drugs, beta-blockers, ACE-inhibitors and anti-platelets, these trends were analyzed separately and no assessment of the potential effect of increasing medication use on case fatality was made.[234]

V.B. Strengths

To our knowledge, this is the first study to present long-term trends in-hospital treatment for both STEMI and NSTEMI patients using validated clinical data. The ARIC community surveillance study offers several advantages in the estimation of in-hospital MI treatment trends, including its large, geographically and racially diverse population, 22-years of followup, population-based sampling scheme, and detailed clinical event data and validated MI diagnostics. Because the ARIC study was conducted over a period of 22 years, 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, because fatal events after myocardial infarction have a complex etiology, it is important to account for the key risk factors that determine survival after MI hospitalization. The ARIC surveillance study collects a large number of clinical covariates that have been shown to affect post-hospitalization mortality, including presence of comorbidities, procedure history, in-hospital complications, and STEMI/NSTEMI classification. This allowed us to account for the presence of potentially important confounders, an integral component to observational analyses of medication use and survival.

Additionally, few studies have compared the performance of propensity scores in analyses of mortality after hospitalization for MI. Even few have examined the behavior of such scores after accounting for use of other medications and procedures. As the use of propensity scores becomes more common in epidemiologic research, we hope that

this study will inform future research concerned with the appropriate use of risk scores in observational cohorts.

V.C. Limitations

This study has a number of limitations. Several reports have underscored the importance of aggressive medical therapy early on in hospitalization for acute MI. One limitation of this analysis is the structure of the medication data element, which captures medications prescribed at any point during hospitalization or at discharge. We did not have information on timing of administration, which limited our ability to make comparisons between early or delayed medication use. We were also unable to distinguish between medication use during hospitalization and at discharge.

An additional limitation of this study is the possibility of confounding by indication. It is possible that the observed increases in medication use over time are due to increasing proportions of patients eligible for each therapy, especially medications which may also be used for other medical conditions besides acute MI (e.g., hypertension, heart failure).[220] Because we do not have data on eligibility for each medication of interest, we were unable to examine the impact of patient-specific indications on temporal trends in MI therapy. However, we did utilize the PREDICT score to account for in-hospital complications and patient comorbidities, which are likely to influence treatment decisions. To assess changes in the comorbidity burden in this population, we analyzed temporal trends in mean PREDICT score, a validated score that includes a comorbidity index and clinical event data. We did not observe significant changes in mean PREDICT score over time for among STEMI or NSTEMI patients.

Because mortality followup in ARIC surveillance is limited to one year after hospital discharge, we were unable to examine the long-term benefits of medical therapies prescribed and administered during the course of hospitalization. It is possible that

benefits conferred by the therapies in our analysis become more or less pronounced with time. However, we did observe general stability in estimates between various timepoints within the one year mortality followup period of our study, so it is unlikely that there would be sudden divergence from the magnitude and/or direction of the observed benefits beginning at one year after hospitalization.

Prior studies have shown less-than-optimal adherence in patients on CHD medication regimens.[227-231] One study of statin therapy in an elderly population documented a decline of nearly 50% in adherence after just 6 months of beginning the medication regimen.[232] We were not able to determine patterns of medication use beyond discharge, and it is likely that each group of subjects identified as taking a particular medication includes a subset of individuals who did not fill prescriptions or were less than 100% adherent to prescribed medication regimens after discharge. However, as data from clinical trials and other observational studies have documented a survival benefit associated with the use of each medical therapy of interest in this analysis, including these patients would presumably reduce the observed effect of the medical therapy analyzed.

Because the ARIC community surveillance study is observational in nature, assignment of patients to medical therapies of interest is not randomized. While we tried to account for major known confounders through the use of propensity scores, it is still possible that unmeasured confounders 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 current study protocol.

Finally, medication and procedure data were abstracted by chart review of sampled events from 4 US communities and may not be representative of practice patterns at all hospitals across the United States.

V.D. Public Health Implications

Results from well-designed clinical trials and observational studies assessing the survival benefits associated with both conventional and innovative cardiovascular medications and procedures have contributed to large improvements in quality of care for hospitalized MI over the past decades. National guidelines put forth by expert panels and organizations are frequently updated to reflect breakthroughs in the study of MI therapies. However, recent studies suggest that there are persistent gaps between available evidence in support of specific therapies and their use in clinical practice at the community level.

The rate at which innovations are implemented in community-based settings varies based on geography, hospital characteristics and provider preferences. Identifying the factors associated with medical therapy use (or lack thereof) is integral to informing interventions aimed at increasing the rate of diffusion and implementation of innovative therapies for MI. As such gaps and their associated factors are identified, policy-makers and hospital administrators will be better equipped to implement changes that are likely to improve the standard of care for hospitalized MI patients.

This project is a cross-sectional community surveillance study of therapy use and mortality in hospitalized MI patients identified over 22 years in 4 U.S. communities. While clinical trial data is often considered the gold standard in the study of medical therapies and survival, such data often represent highly-selected patient groups, and thus may not be generalizable to the population of hospitalized MI in the community. The present study included a geographically and racially diverse population of patients followed over a long period of time, and the results will have implications for a broader patient population than is often possible with highly-selected clinical trial groups.

All observational studies have a significant caveat: differences in underlying mortality risk between treated and untreated patients and confounding by indication are more likely to be present when patients are not randomized to a particular treatment. However, the use of propensity scores helps to minimize the potential bias introduced by these differences. Additionally, we used a number of different PS strategies in a community-based population may help to inform future research efforts analyzing outcomes in non-randomized patient populations.

Better medical care in the US is leading to lower case fatality rates for a number of acute events and longer life expectancy for those living with chronic conditions. Thus, the proportion of MI patients with a history of cardiovascular disease or who are living with other comorbidities is rising. Clinical management of MI becomes particularly complex when treating patients with a number of other medical problems or patients of advanced age. We documented a rising number of medications prescribe during hospitalization from 1987-2008. As the proportion of MI patients receiving multiple medications during hospitalization continues to rise, it become increasingly important to account for the effect of all therapies when analyzing the survival benefit of a particular medication or revascularization procedure. In this study, we analyzed the effect of other medications and revascularization procedures by creating a number of different propensity scores reflecting the number and type of other medical therapies

V.E. Future directions

The rate of implementation of medical innovation is not consistent across all hospitals treating acute MI. Certain providers may apply scientific advances to the clinical care of MI more rapidly than others, which may result in disparities in care for MI patients. Additionally, there is an increasing variety of medical therapy options for acute MI, and the decision to use one over another may depend on a number of factors,

including provider preferences, patient frailty and life expectancy, comorbidities, insurance coverage, and hospital resources. Future studies should examine barriers to providing state-of-the-art care for MI and evaluate strategies to improve compliance with changing national guidelines.

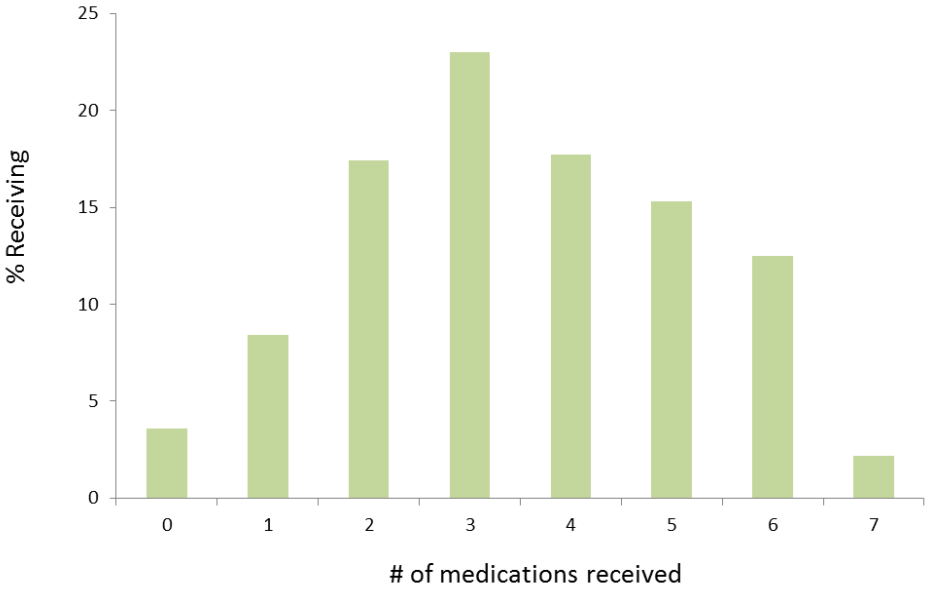
A number of reports have documented less-than-perfect adherence to medication regimens following MI hospitalization. Future studies should evaluate factors associated with adherence to both pharmaceutical regimens and lifestyle recommendations in patients following acute MI. Education efforts targeting risk factors for recurrent MI and other cardiovascular diseases should be rigorously evaluated to determine the most cost-effective and efficacious strategies for reducing the risk of a future MI event.

Finally, new methods in comparative effectiveness analysis, the field of study in which one treatment is evaluated in comparison to at least one other established treatment in an attempt to assess their effectiveness relative to one another, hold promise for informing providers faced with a variety of treatment options. Results from these studies, along with those from cost-benefit analyses, will continue to inform patients and providers of the most safe, effective, and economic medical therapies available for the treatment of acute MI.

APPENDICES

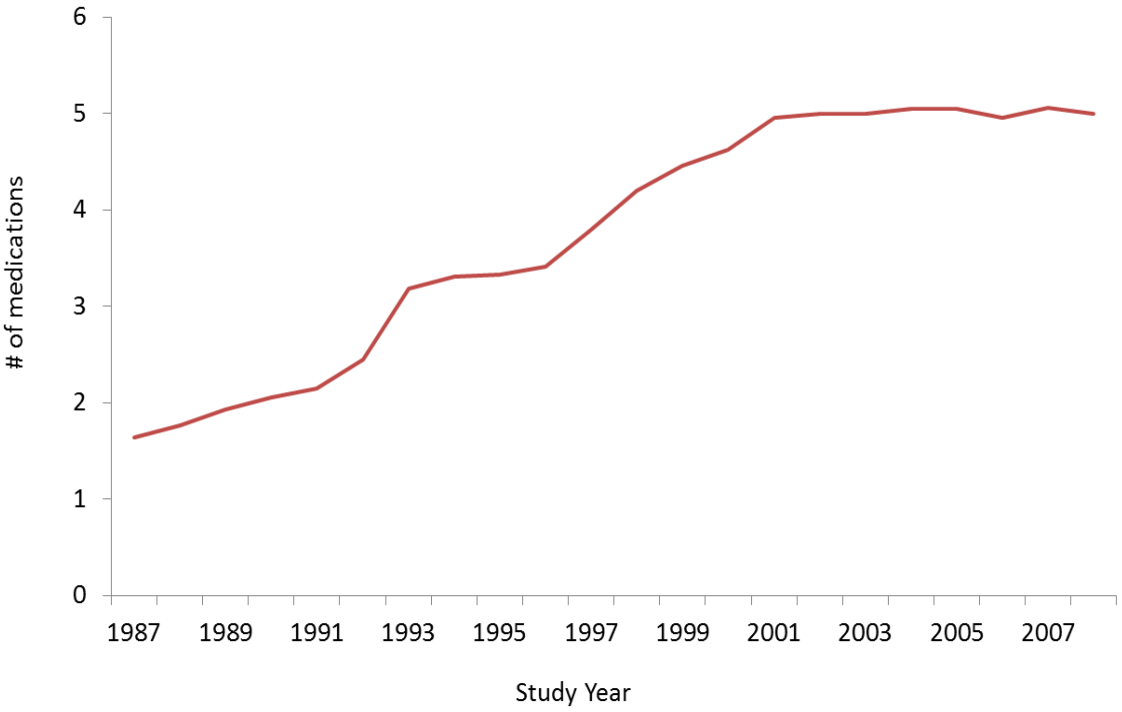
Appendix A: Supplemental Tables and Figures

Figure S.1.1 Percentage of patients* . . . . . ng discreet numbers of medications†: The ARIC Community Surveillance Study (1987 – 2008).



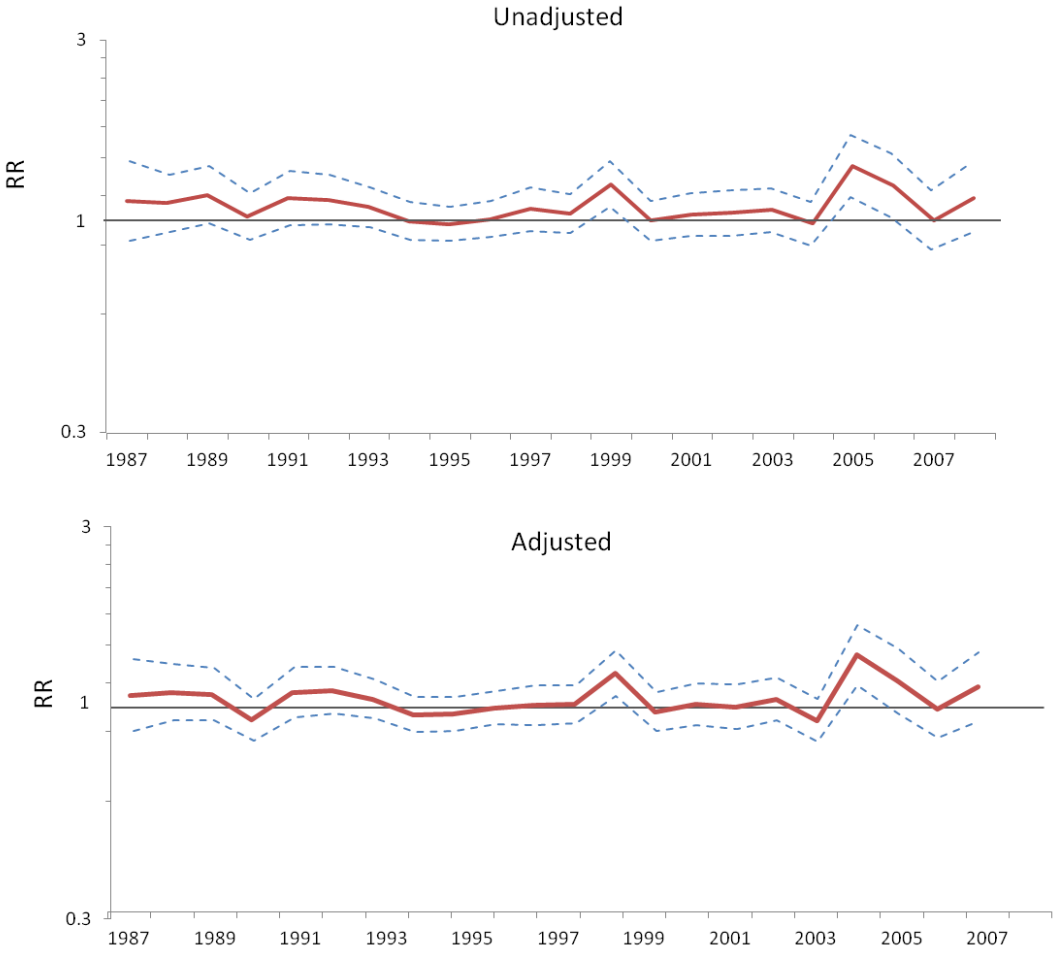
*Weighted percentage of definite/probable MI events
† Medication or procedure use at any point during hospitalization

Figure S.1.2. Average number of medications* administered per event†: The ARIC Community Surveillance Study (1987 – 2008).



*Medication use at any point during hospitalization
†Weighted number of definite/probable MI events

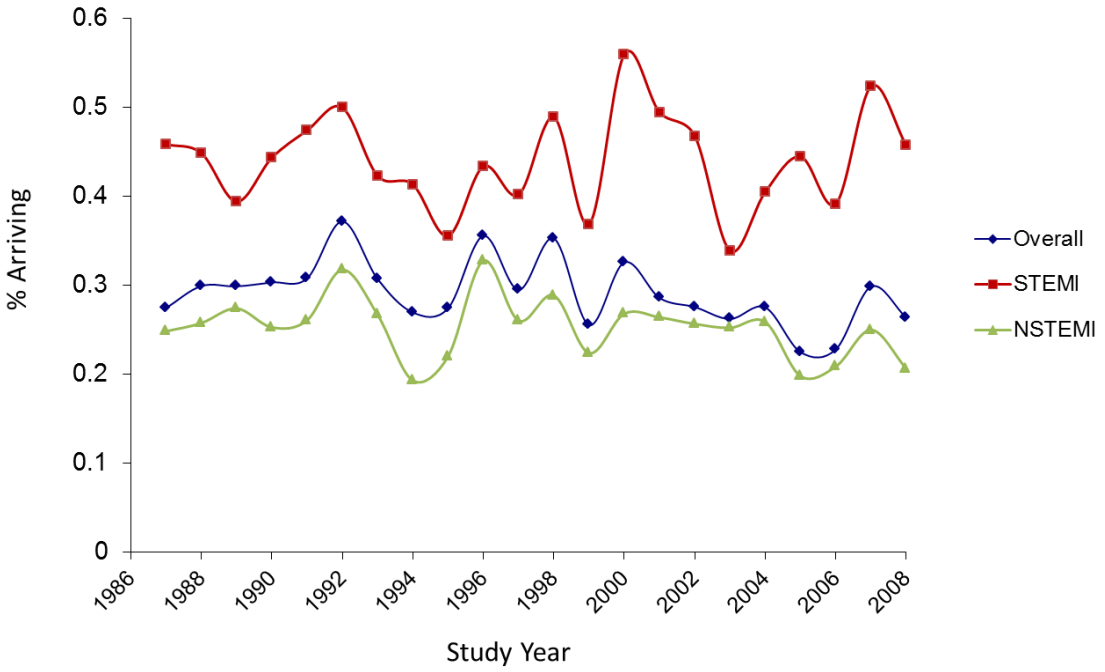
Figure S.1.3. Unadjusted and adjusted risk ratios for receipt of any reperfusion procedures for men compared to women in patients receiving angiography: The ARIC Community Surveillance Study (1987 – 2008).



*Eligible reperfusion strategies included IV-tPA, PCI with or without stents, and CABG

† Weighted loglinear regression adjusting for age, race*center, PREDICT score, and STEMI classification

Figure S.1.4 Patients arriving within 2 hours of symptom onset * by STEMI classification† and study year: The ARIC Community Surveillance Study (1987 – 2008).



*Time interval from symptom onset to hospital arrival
†Definite and probable MIs classified as STEMI/NSTEMI by biomarker values and pain presentation

Table S.1.1. Medication and procedure use by year in definite and probable MI patients in the ARIC Community Surveillance Study: 1987 – 2008*.

	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Medications‡																						
Aspirin	56	61	78	79	85	87	85	92	89	89	89	93	90	91	90	92	89	89	92	88	94	87
BB	54	42	51	57	62	63	64	69	68	71	71	75	79	83	87	86	89	86	85	92	86	90
CCB	70	68	66	67	62	57	62	57	46	47	33	33	23	29	21	25	23	22	25	22	20	24
ACEI	---	---	---	---	---	13	26	38	37	44	46	61	59	64	66	72	69	69	70	66	68	72
Heparin	---	---	---	---	---	26	71	76	77	81	77	76	72	63	77	76	63	71	65	70	77	76
NonAAP	---	---	---	---	---	---	---	---	--	---	41	47	52	50	60	73	71	69	71	55	69	58
Lipid-lowering	---	---	---	---	---	---	---	---	---	---	---	30	50	64	63	70	69	76	79	70	74	69
Procedures																						
t-PA	17	21	24	25	28	28	24	22	18	19	20	14	12	10	8	9	3	1	1	0.5	0.5	0.8
PCI	15	15	24	20	29	27	25	32	29	28	32	35	36	33	39	48	46	47	47	39	43	37
CABG	17	14	15	17	16	15	16	12	15	18	12	13	15	15	9	12	9	5	7	8	7	7
Stent	---	---	---	---	---	---	---	---	--	---	---	9	22	23	27	27	29	24	38	35	33	18
Any procedure	39	38	51	48	56	54	51	52	52	54	52	53	55	51	49	62	55	54	52	44	48	44

* Medication information not collected during selected years indicated by dashed lines (---)

† Loglinear regression models age-standardized to 200 US Census population

‡ Abbreviations: ACEI=ACE Inhibitors; Non-AAP=non-aspirin anti-platelets; BB=Beta Blockers; ASA=aspirin; CCB=calcium-channel blockers; PCI=Percutaneous Coronary intervention; Any rep= Any reperfusion (CABG, PCI, Stent, T-PA); CABG = Coronary artery bypass graft; t-PA = tissue plasminogen activator

Table S.1.2. STEMI: Use of medical therapy and revascularization procedures overall and by event year groups in the ARIC Community Surveillance Study, 1987-2008*.

Therapy	Overall N=6106[†] (%)[§]	1987-1991‡ N=1475 (%)	1992-1996 N=1926 (%)	1997-2001 N=1420 (%)	2002-2008 N=1284 (%)
Medication					
Aspirin	89.6 (0.39)	77.9 (1.08)	91.1 (0.65)	93.5 (0.66)	96.2 (0.53)
BB	75.6 (0.55)	57.0 (1.29)	73.4 (1.01)	82.9 (1.00)	92.2 (0.75)
CCB	37.4 (0.62)	60.6 (1.27)	44.6 (1.13)	26.5 (1.17)	12.2 (0.91)
ACEI	42.6 (0.63)	---	35.7 (1.09)	63.7 (1.28)	78.3 (1.15)
Heparin	60.3 (0.63)	---	74.9 (0.99)	86.0 (0.92)	78.1 (1.15)
Lipid-lowering medication	26.3 (0.56)	---	---	37.1 (1.28)	84.0 (1.02)
Non-aspirin anti-platelets	31.9 (0.60)	---	---	59.0 (1.31)	84.3 (1.02)
Procedures					
Thrombolytics	33.9 (0.61)	44.1 (1.29)	45.6 (1.13)	33.1 (1.25)	5.4 (0.63)
PCI	42.6 (0.63)	24.2 (0.01)	34.4 (1.08)	47.0 (1.32)	71.1 (1.27)
CABG	14.9 (0.46)	15.3 (0.94)	18.5 (0.89)	15.7 (0.96)	8.0 (0.76)
Stent	20.5 (0.52)	---	---	29.1 (1.21)	65.1 (1.33)

* Medication information for ACEI, Heparin, Lipid-lowering drugs, non-aspirin anti-platelets, and stents not collected during years indicated by dashed lines (---)

† Weighted number of definite or probable MI events

‡ Chi-square test for independence with Taylor Series variance estimation significant for all variables at $p < 0.001$

§ Percentages calculated using years in which data was collected for each therapy

Table S.1.3. NONSTEMI: Use of medical therapy and revascularization procedures overall and by event year groups in the ARIC Community Surveillance Study, 1987-2008*.

Therapy	Overall N=20302[†] (%)[§]	1987-1991‡ N=4970 (%)	1992-1996 N=4439 (%)	1997-2001 N=4869 (%)	2002-2008 N=6023 (%)
Medication					
Aspirin	81.8 (0.27)	63.5 (0.68)	84.7 (0.54)	88.3 (0.46)	89.4 (0.40)
BB	67.1 (0.33)	43.0 (0.70)	57.9 (0.74)	74.9 (0.62)	87.5 (0.43)
CCB	45.9 (0.35)	67.9 (0.66)	59.2 (0.74)	34.5 (0.68)	27.1 (0.57)
ACEI	40.6 (0.34)	---	31.0 (0.69)	57.9 (0.71)	66.6 (0.61)
Heparin	50.9 (0.35)	---	60.8 (0.73)	69.5 (0.66)	70.3 (0.59)
Lipid-lowering medication	30.8 (0.32)	---	---	41.3 (0.71)	70.4 (0.59)
Non-aspirin anti-platelets	28.4 (0.32)	---	---	44.1 (0.71)	59.5 (0.63)
Procedures					
Thrombolytics	5.7 (0.16)	9.5 (0.42)	8.7 (0.42)	4.8 (0.31)	1.0 (0.13)
PCI	24.5 (0.30)	13.5 (0.48)	20.9 (0.61)	27.0 (0.64)	34.3 (0.61)
CABG	14.0 (0.24)	15.9 (0.52)	17.8 (0.57)	13.7 (0.49)	9.8 (0.38)
Stent	13.3 (0.24)	---	---	17.9 (0.55)	30.5 (0.59)

* Medication information for ACEI, Heparin, Lipid-lowering drugs, non-aspirin anti-platelets, and stents not collected during years indicated by dashed lines (---)

† Weighted number of definite or probable MI events

‡ Chi-square test for independence with Taylor Series variance estimation significant for all variables at $p < 0.001$

§ Percentages calculated using years in which data was collected for each therapy

Table S.2.1 Inverse probability of treatment weighed risk ratios for medical therapy use* and 30-day mortality† among hospitalized MI patients by propensity score (PS) analytic strategy: The ARIC community surveillance study (1987-2008).

	Model B. PS Only‡		Model C. PS + all other medical therapies§		Model D. PS + number of other therapies (categorical**)		Model E. PS + number of other therapies (continuous	
Therapy	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Medication								
Beta-blockers	0.70	0.61, 0.81	0.75	0.66, 0.87	0.79	0.68, 0.92	0.84	0.69, 1.01
Calcium channel blockers	0.88	0.77, 1.01	0.90	0.79, 1.04	0.87	0.75, 1.01	1.07	0.88, 1.30
Aspirin	0.69	0.60, 0.81	0.72	0.62, 0.83	0.71	0.62, 0.82	0.87	0.72, 1.05
Lipid-lowering medications	0.62	0.49, 0.79	0.72	0.55, 0.94	0.70	0.51, 0.96	0.99	0.71, 1.37
Non-aspirin anti-platelets	0.79	0.63, 0.98	0.99	0.77, 1.26	0.98	0.75, 1.27	1.33	1.00, 1.76
Heparin	0.89	0.76, 1.04	1.02	0.87, 1.20	1.03	0.86, 1.23	1.14	0.91, 0.91
ACE Inhibitors	0.70	0.60, 0.82	0.74	0.63, 0.87	0.75	0.63, 0.89	0.85	0.69, 1.05
Reperfusion								
CABG	0.65	0.54, 0.78	0.68	0.53, 0.88	0.67	0.54, 0.82	0.76	0.61, 0.94
Angioplasty	0.52	0.44, 0.63	0.58	0.46, 0.72	0.59	0.49, 0.72	0.74	0.60, 0.91
IV t-PA	0.64	0.50, 0.83	0.78	0.61, 0.99	0.63	0.49, 0.80	0.63	0.50, 0.80
Stent	0.57	0.43, 0.76	0.69	0.49, 0.98	0.59	0.43, 0.83	0.76	0.55, 1.05

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

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

‡ 5% of full propensity score range was trimmed from maximum values among untreated patients and minimum values among treated patients after elimination of non-overlapping scores

§ Indicator variables representing 4 highest quintiles of propensity score values calculated separately for treated and untreated patients after eliminating non-overlapping scores and trimming

**Medication number was categorized as <3 and 3+

Table S.2.2 Inverse probability of treatment weighed risk ratios for medical therapy use* and 90-day mortality† among hospitalized MI patients by propensity score (PS) analytic strategy: The ARIC community surveillance study (1987-2008).

	Model B. PS Only‡		Model C. PS + all other medical therapies§		Model D. PS + number of other therapies (categorical**)		Model E. PS + number of other therapies (continuous	
Therapy	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Medication								
Beta-blockers	0.74	0.68, 0.81	0.80	0.70, 0.92	0.83	0.71, 0.95	0.83	0.69, 0.99
Calcium channel blockers	0.94	0.82, 1.08	0.97	0.85, 1.12	0.92	0.79, 1.06	1.10	0.92, 1.31
Aspirin	0.72	0.61, 0.83	0.76	0.66, 0.87	0.75	0.65, 0.85	0.89	0.74, 1.06
Lipid-lowering medications	0.67	0.52, 0.85	0.81	0.61, 1.07	0.78	0.56, 1.08	0.98	0.71, 1.34
Non-aspirin anti-platelets	0.78	0.63 ,0.97	0.95	0.76, 1.20	0.96	0.72, 1.27	1.27	0.95 ,1.70
Heparin	0.91	0.78, 1.06	1.04	0.89, 1.21	1.04	0.88, 1.23	1.13	0.92, 1.39
ACE Inhibitors	0.73	0.63, 0.85	0.78	0.67, 0.90	0.79	0.67, 0.93	0.86	0.71 ,1.05
Reperfusion								
CABG	0.69	0.56, 0.83	0.74	0.58, 0.95	0.59	0.43, 0.83	0.80	0.63, 1.01
Angioplasty	0.51	0.43, 0.61	0.56	0.45, 0.69	0.69	0.56, 0.86	0.67	0.55, 0.82
IV t-PA	0.61	0.48, 0.78	0.76	0.60, 0.96	0.56	0.46, 0.67	0.62	0.50, 0.77
Stent	0.74	0.68, 0.81	0.80	0.70, 0.92	0.83	0.71, 0.95	0.83	0.69, 0.99

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

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

‡ 5% of full propensity score range was trimmed from maximum values among untreated patients and minimum values among treated patients after elimination of non-overlapping scores

§ Indicator variables representing 4 highest quintiles of propensity score values calculated separately for treated and untreated patients after eliminating non-overlapping scores and trimming

**Medication number was categorized as <3 and 3+

Table S.2.3 Inverse probability of treatment weighed risk ratios for medical therapy use* and 365-day mortality† among hospitalized MI patients by propensity score (PS) analytic strategy: The ARIC community surveillance study (1987-2008).

	Model B. PS Only‡		Model C. PS + all other medical therapies§		Model D. PS + number of other therapies (categorical**)		Model E. PS + number of other therapies (continuous	
Therapy	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Medication								
Beta-blockers	0.72	0.63, 0.82	0.76	0.67, 0.87	0.78	0.68, 0.90	0.85	0.72, 1.00
Calcium channel blockers	0.93	0.82, 1.05	0.95	0.84, 1.09	0.91	0.79, 1.04	1.08	0.91, 1.27
Aspirin	0.67	0.58, 0.78	0.75	0.65, 0.86	0.73	0.64 ,0.83	0.88	0.74, 1.05
Lipid-lowering medications	0.68	0.55, 0.85	0.82	0.64, 1.05	0.80	0.60, 1.06	1.00	0.74, 1.35
Non-aspirin anti-platelets	0.80	0.65, 0.98	1.00	0.80, 1.25	1.01	0.79, 1.29	1.28	0.98, 1.66
Heparin	0.91	0.79, 1.05	0.96	0.83, 1.11	1.05	0.90, 1.24	1.23	1.01, 1.50
ACE Inhibitors	0.74	0.64, 0.86	0.79	0.68, 0.91	0.79	0.67, 0.92	0.89	0.74, 1.07
Reperfusion								
CABG	0.64	0.53, 0.77	0.72	0.57, 0.91	0.66	0.54, 0.81	0.76	0.61, 0.94
Angioplasty	0.51	0.44, 0.61	0.55	0.45, 0.68	0.56	0.47, 0.67	0.67	0.56, 0.81
IV t-PA	0.59	0.46, 0.74	0.73	0.59, 0.92	0.59	0.47, 0.74	0.60	0.49, 0.74
Stent	0.55	0.43 ,0.71	0.66	0.49, 0.89	0.57	0.43, 0.76	0.71	0.53, 0.95

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

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

‡ 5% of full propensity score range was trimmed from maximum values among untreated patients and minimum values among treated patients after elimination of non-overlapping scores

§ Indicator variables representing 4 highest quintiles of propensity score values calculated separately for treated and untreated patients after eliminating non-overlapping scores and trimming

**Medication number was categorized as <3 and 3+

Figure S.2.1 Mean propensity scores by quintile in treated and untreated patients for each medication of interest: The ARIC Community Surveillance Study (1987 – 2008).

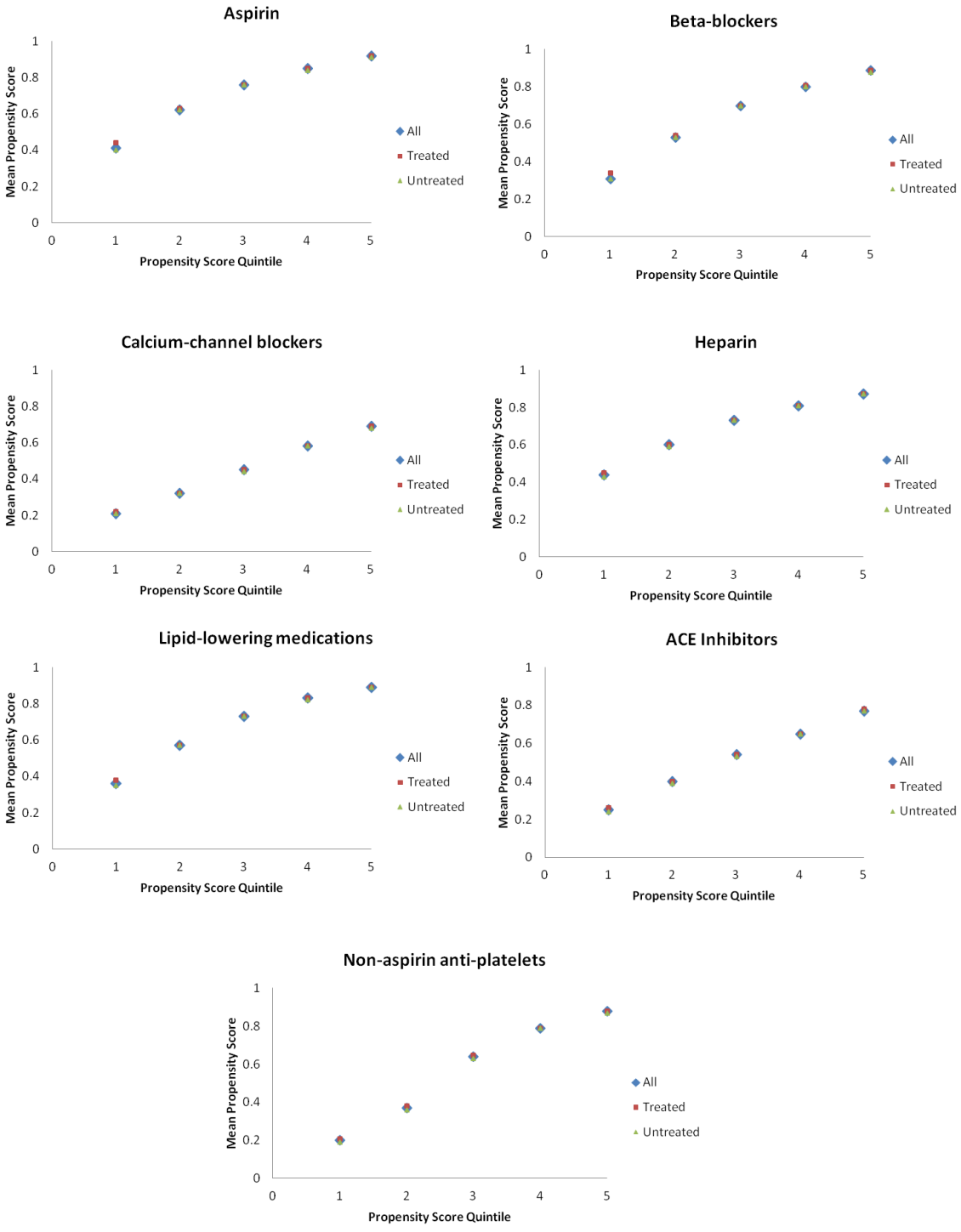


Figure S.2.2 Mean propensity scores by quintile in treated and untreated patients for each reperfusion strategy of interest: The ARIC Community Surveillance Study (1987 – 2008).

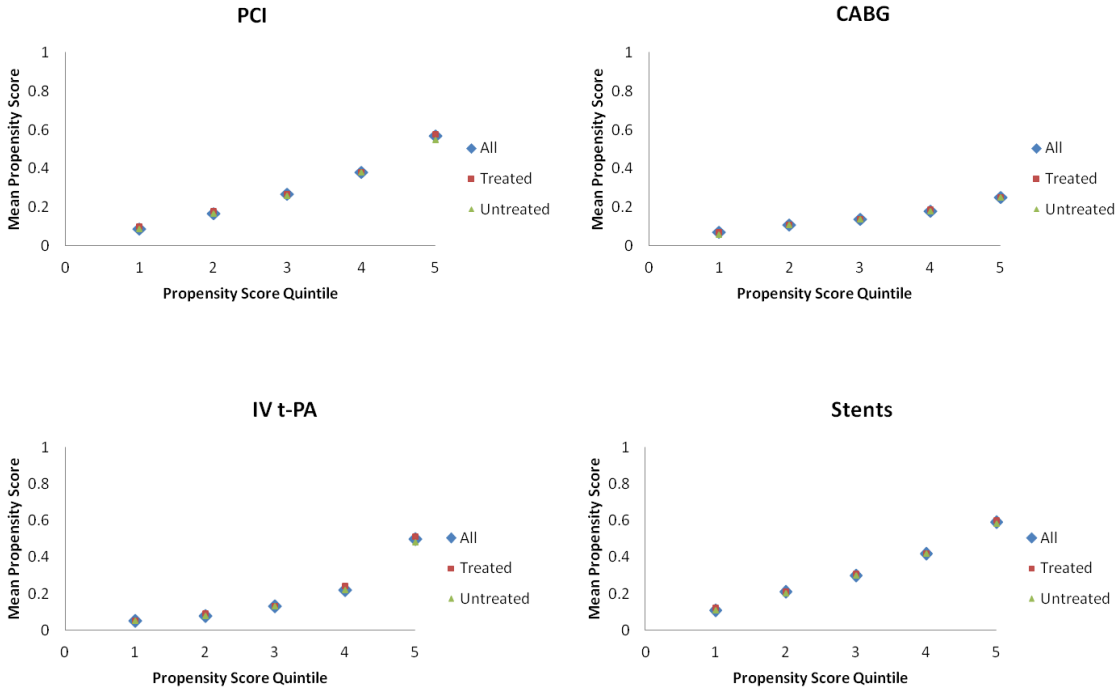


Table S.2.4. Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with Calcium-Channel Blockers in Propensity Score Quintiles: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	78.1	74.9	63.8	57.1	64.1	66	70.1	74	51.6	54.6
Race Classification										
Forsyth Black	6.8	8.6	13.6	16	9.6	9.4	10.5	8.9	12.7	11.3
Forsyth White	20	17.6	32	26	30	27.6	25.5	31.2	30.8	38.5
Jackson Black	15.5	18.1	15.8	18.1	10.3	10.7	9	7.7	13.5	8.8
Jackson White	5.5	4.9	8.8	8.3	9.4	9.7	11.7	12	17.3	18.8
Washington Whites	19.8	21.2	15.5	15.7	17.6	19.2	20.3	19.3	17.3	14.3
Minnesota Whites	32.4	29.6	15.3	15.8	23.2	23.6	23	21	8.4	8.3
Comorbidities										
Prior MI	19.1	23.9	31.5	32.2	35.3	35.6	35.3	33.5	42.9	42.4
Diabetes	21	28	37.6	41.4	35.9	30.6	18.2	16.7	14.9	12.5
Never Smoking	24.2	27.8	34.6	35.5	48.9	48.2	63.6	61.2	88	90.8
Cardiogenic Shock	4.1	5.2	2.3	2	5	5.7	5.3	3.2	1	1.2
CHF	26.3	37.4	27.3	34.5	31.4	33.3	33.7	30.8	41.8	25.7
Cardiac Arrest	11.6	19.2	6.7	6.6	13.8	13.4	15.9	10.5	5.8	3.1
STEMI	30.9	22.4	13.5	12.5	28.1	30.2	19.2	22.3	4.8	5.8
Study Year										
1987-1991	0.0	0.0	0.3	0.4	8.5	11.7	38.7	38.2	74.4	75.7
1992-1996	0.3	0.5	5.7	4.6	45.6	48.6	59.8	60.8	25.6	24.3
1997-2001	25.5	28.3	50.9	52.9	39.1	35.3	1.5	1	0	0
2002-2008	74.2	71.3	43.1	42.1	6.8	4.4	0	0	0	0
Prior PCI	10.2	9.9	20.3	18.7	17.1	15.5	7.7	9.1	8.3	10.4
Prior CABG	6.8	7.7	17.7	18.5	20.3	16.8	11.7	13.5	17.2	17.6

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails of the overlapping distribution

†Treated at any point during hospitalization or at discharge

Table S.2.5 Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with Beta-Blockers in Propensity Score Quintiles*: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	58.4	60.1	63.2	63.7	64.6	65.3	69.8	69	66.9	69.2
Race Classification										
Forsyth Black	13.2	11.6	9.3	12.4	11.9	10.8	9.3	8.9	9	9.3
Forsyth White	22.9	23.9	24.3	22.8	32.5	31	33.1	31.9	28.1	31.4
Jackson Black	15.4	14.1	14.2	13.5	13.6	14.9	9.4	11.8	9.8	9.1
Jackson White	17.8	23.6	14.8	13	13.8	10.7	7.8	7.3	8	4.8
Washington Whites	21.6	16.6	18	16.2	14.7	18.5	15.4	17.2	14	17.9
Minnesota Whites	9.2	10.2	19.5	22.2	13.5	14.1	24.9	22.9	31.1	27.5
Comorbidities										
Prior MI	42.3	42.4	38.2	35.3	31.7	31.4	25.5	29.4	27.4	29.4
Diabetes	13.5	12.5	25.9	26.3	25.1	25.6	23.7	30.7	34.1	29.1
Never Smoking	80.4	80.6	54.6	58.1	57.7	52.3	45.3	42	37.9	31.7
Cardiogenic Shock	6.7	6.3	4.8	4.5	2.9	2.3	1.9	2.4	2.5	1.4
CHF	63.9	51.1	39.2	38.6	29.3	31	20.3	24.9	9.1	12.3
Cardiac Arrest	22.9	19.1	12	14.3	9.6	8.8	6.2	4.3	4.2	3.3
STEMI	9.6	12	15	15.4	19.7	17.1	22.9	24.2	22.3	25.6
Study Year										
1987-1991	66.3	66.2	28.6	29.2	31.4	26.2	13.9	9.2	0	0
1992-1996	30.9	28.7	39.9	43	22.3	22.9	37.6	37.7	14.6	10.4
1997-2001	2.8	5.1	30.3	24.6	33.3	34.5	19.3	19.9	34.8	49.6
2002-2008	0	0	1.3	3.1	13	16.5	29.1	33.2	50.6	39.9
Prior PCI	2.7	4	8	8.3	10	10.3	12.5	16.7	24.5	21.1
Prior CABG	10.7	13.1	18.1	16.3	15.1	14.4	12.4	16.5	17.6	16

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails of the overlapping distribution

†Treated at any point during hospitalization or at discharge

Table S.2.6. Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with Aspirin in Propensity Score Quintiles*: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	51.3	54.4	57.3	60.6	59.4	56	68.8	65.6	70.8	72.4
Race Classification										
Forsyth Black	10.2	11	13.4	10.5	10.7	13.1	18.9	16.7	11.2	10.3
Forsyth White	14.1	13.7	22	21.5	14	16.7	26.7	25.7	39.2	35
Jackson Black	17.7	16.2	15.3	16.6	28.4	23.6	9.7	14.5	3.9	6.1
Jackson White	15.8	17.8	12.9	15.2	12.9	10.8	8.8	7.7	10.7	12
Washington Whites										
Minnesota Whites	13.3	12	18.8	20	15.1	14.6	17.3	21.5	24.5	23.3
Comorbidities										
Prior MI	38.4	38.5	35	39.9	30.8	32.8	33.5	35.6	57.9	41.4
Diabetes	6.9	12	21	20.2	30.4	39.2	40.8	36	42.4	21.3
Never Smoking	93.4	88.2	82	80.4	50.8	50.1	32.1	30.2	29.5	49.6
Cardiogenic Shock	10.3	8.9	3	4.1	4.1	2.4	2.9	1.9	8.5	5.5
CHF	65.4	59.8	36.7	40.1	50.2	49.8	30.2	27.5	20.3	23.3
Cardiac Arrest	41.4	35.8	18.9	16.2	5	4.5	6.3	4.2	14.9	12.8
STEMI	9.4	8.9	12	13.2	9.3	8.6	10.4	11.7	14.6	17.4
Study Year										
1987-1991	---	---	---	---	---	---	---	---	---	---
1992-1996	10.1	11.8	25.6	28.1	9.3	37.6	22	21.3	15.2	13.3
1997-2001	3.4	5.4	11.9	11.1	39.2	26.3	32.8	33.6	22.3	25.6
2002-2008	3.3	6.3	12.2	10.4	28.8	29.6	41.8	41	45.5	24.3
Prior PCI	1.5	1.2	4.9	5.1	23.9	6.1	11.1	16.2	35.2	27.3
Prior CABG	4.8	3.9	11.4	16.4	12	11.4	22.4	19.8	36.1	31

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails of the overlapping distribution

†Treated at any point during hospitalization or at discharge

Table S.2.7. Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with ACE Inhibitors in Propensity Score Quintiles*: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	67.0	66.2	64.8	64.4	66.0	64.7	66.3	64.7	64.5	68.2
Race Classification										
Forsyth Black	5.1	4.5	8.8	6.6	7.3	9.4	10.8	11	18.9	21.9
Forsyth White	33.7	30.1	31.8	32.5	31.1	32.2	33	30.6	19.1	19
Jackson Black	4.3	8.3	7.5	8.9	9.4	10.7	12.8	12.3	27.9	27.7
Jackson White	13.4	18.6	10.8	12.6	11.1	7.1	8.2	7.3	5.3	4.2
Washington Whites	22.9	18.3	20.6	19	20	19.1	13.2	16.6	9.6	9.7
Minnesota Whites	30.5	20.3	20.4	20.4	21.1	21.5	21.9	22.2	19.1	17.5
Comorbidities										
Prior MI	24.1	25.9	31.9	30.6	27.7	26.7	29.4	31.3	38	40
Diabetes	9.6	21.3	22.5	25.9	22.5	25.5	37.6	33.2	62.1	60.2
Never Smoking	51.4	45.1	39.9	42	35.7	40.5	27.1	29.6	28	23.8
Cardiogenic Shock	3.1	3.4	3.3	4	2.6	2.9	3	2	2.8	2.8
CHF	8.4	13.2	26.2	35	18.1	21.2	26.5	25	60	54.1
Cardiac Arrest	12.4	16.7	13.2	12.9	7.9	8.3	8.9	6.4	5.5	3.1
STEMI	14.9	13.8	26.1	20.1	14.1	15.6	20.3	21.1	20.1	24.7
Study Year										
1987-1991										
1992-1996	98.1	98.1	66.1	60.4	15.2	17.9	3.1	4.4	0.4	0.4
1997-2001	1.9	1.8	27.5	35	56.3	50.4	44.5	38.8	27.7	28.2
2002-2008	0	0.1	6.4	4.6	28.5	31.7	52.4	56.8	72	71.4
Prior PCI	10.2	7.8	12.3	11.5	16.2	13.1	15.5	20.2	20.6	23.3
Prior CABG	12.8	14.5	13.2	15.8	15.6	15.2	16.0	16.0	20.8	19.4

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails of the overlapping distribution

†Treated at any point during hospitalization or at discharge

Table S.2.8. Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with Lipid-Lowering Medications in Propensity Score Quintiles*: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	52.5	49.3	59.9	61.2	68.2	70.6	74.6	67.6	71.7	74.6
Race Classification										
Forsyth Black	14.2	10.1	12.1	15.0	13.6	12.3	6.4	7.7	9.9	12.2
Forsyth White	19.2	24.3	25.1	24.0	29.3	29.3	35.5	33.8	36.0	31.8
Jackson Black	27.6	27.2	19.7	21.1	11.1	12.4	12.0	11.5	11.5	8.7
Jackson White	9.4	11.2	8.0	6.6	10.7	6.4	7.5	7.7	2.4	3.1
Washington Whites	11.8	14.5	18.4	14.2	16.0	18.1	16.5	18.2	14.7	15.5
Minnesota Whites	17.7	12.8	16.7	19.1	19.2	21.5	22.0	21.1	25.5	28.6
Comorbidities										
Prior MI	17.7	19.7	26.6	29.1	33.8	37.1	34.6	25.8	27.8	19.2
Diabetes	37.7	42.7	39.5	42.9	32.2	29.7	40.2	31.6	37.9	35.8
Never Smoking	38.7	42.4	36.7	35.6	29.2	29.8	38.5	36.8	32.9	26.7
Cardiogenic Shock	5.4	5.5	3.0	1.9	2.9	2.8	2.3	1.6	0.7	0.4
CHF	64.2	55.8	30.9	33.3	21.0	18.8	13.8	20.0	7.6	5.0
Cardiac Arrest	24.9	16.0	6.8	5.7	4.1	7.1	1.6	1.6	0.5	0.4
STEMI	9.6	7.7	7.8	7.8	19.2	15.1	17.6	21.1	23.3	30.4
Study Year										
1987-1991	---	---	---	---	---	---	---	---	---	---
1992-1996	---	---	---	---	---	---	---	---	---	---
1997-2001	60.8	61.3	22.8	27.7	59.4	49.6	41.0	30.6	14.0	7.1
2002-2008	39.2	38.7	77.2	72.3	40.6	50.4	59.0	69.4	86.0	92.9
Prior PCI	5.1	5.8	13.8	16.9	19.3	24.2	29.1	20.5	20.5	16.7
Prior CABG	3.1	6.0	14.2	16.1	21.6	23.9	21.6	16.4	18.8	8.6

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails of the overlapping distribution

†Treated at any point during hospitalization or at discharge

Table S.2.9 Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with Non-Aspirin Anti-Platelets in Propensity Score Quintiles*: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	58.3	60.8	62.8	61.1	64.0	65.3	72.0	70.6	65.1	71.3
Race Classification										
Forsyth Black	14.5	13.9	15.0	14.4	9.9	10.8	10.9	8.5	6.0	10.3
Forsyth White	19.5	28.1	24.9	22.6	28.8	30.3	33.2	37.2	44.9	30.8
Jackson Black	23.7	22.8	19.8	19.8	11.3	11.8	10.1	7.7	12.2	10.1
Jackson White	10.5	7.2	7.1	7.3	9.7	10.5	5.4	6.5	3.6	5.8
Washington Whites	16.1	13.7	14.6	19.3	19.8	17.4	18.3	15.4	15.5	16.7
Minnesota Whites	15.7	14.4	18.6	16.5	20.6	19.3	22.1	24.7	17.8	26.4
Comorbidities										
Prior MI	32.8	34.1	29.8	38.1	36.1	25.0	31.6	22.7	22.1	18.9
Diabetes	43.8	45.8	38.2	42.7	39.7	34.2	28.1	22.9	34.0	30.0
Never Smoking	38.1	35.1	34.7	32.9	29.3	32.8	30.5	30.7	27.9	34.3
Cardiogenic Shock	2.6	3.1	2.3	2.3	4.7	3.3	2.6	2.9	1.1	2.0
CHF	47.9	38.1	28.5	33.6	32.7	26.9	25.2	17.0	7.3	7.3
Cardiac Arrest	11.7	13.7	6.7	5.1	8.7	7.9	4.7	5.3	3.4	4.1
STEMI	9.0	5.9	7.0	8.7	17.1	16.9	31.5	31.8	17.7	20.8
Study Year										
1987-1991	---	---	---	---	---	---	---	---	---	---
1992-1996	---	---	---	---	---	---	---	---	---	---
1997-2001	83.1	79.3	19.8	14.8	66.4	76.5	69.4	76.0	13.5	4.9
2002-2008	16.9	20.7	80.2	85.2	33.6	23.5	30.6	24.0	86.5	95.1
Prior PCI	7.9	8.6	20.4	23.9	25.1	19.0	15.3	15.4	18.5	16.0
Prior CABG	15.7	17.2	22.1	24.5	18.8	16.0	13.0	9.9	9.5	9.9

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails

†Treated at any point during hospitalization or at discharge

Table S.2.10. Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with Heparin in Propensity Score Quintiles*: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	58.9	55.5	62.6	65.0	69.8	68.4	68.9	70.5	69.1	71.3
Race Classification										
Forsyth Black	12.3	12.6	15.1	17.2	8.3	5.0	5.5	7.8	12.8	11.0
Forsyth White	13.9	11.5	27.3	31.1	26.7	21.9	26.7	32.3	37.8	45.9
Jackson Black	22.7	25.2	17.6	16.4	4.2	6.8	8.3	9.9	20.9	7.9
Jackson White	12.0	13.4	8.8	7.7	5.9	7.8	9.1	11.1	12.3	7.6
Washington Whites	7.2	4.4	18.9	19.6	25.1	18.1	12.6	12.0	7.0	22.2
Minnesota Whites	31.9	32.9	12.2	8.1	29.6	40.3	37.8	26.8	9.1	5.4
Comorbidities										
Prior MI	40.9	40.7	36.3	34.3	30.8	32.3	26.2	25.4	21.3	22.4
Diabetes	27.8	34.4	43.0	40.4	33.8	32.8	22.0	21.9	28.9	27.2
Never Smoking	61.9	61.2	26.3	25.6	51.4	43.5	44.5	40.4	18.9	18.4
Cardiogenic Shock	1.7	2.0	2.8	2.5	4.1	5.0	1.8	2.8	3.6	2.2
CHF	49.4	45.6	39.1	35.4	21.8	24.9	15.0	20.3	12.6	16.1
Cardiac Arrest	12.8	12.8	10.7	9.3	7.5	9.1	5.6	7.4	5.6	5.3
STEMI	4.3	7.2	8.6	10.2	21.8	20.4	24.9	22.5	35.1	32.3
Study Year										
1987-1991	---	---	---	---	---	---	---	---	---	---
1992-1996	56.8	46.6	27.3	21.4	36.6	42.1	31.7	41.7	11.9	21.8
1997-2001	18.9	21.3	37.9	35.7	30.7	28.5	23.8	26.9	34.8	38.0
2002-2008	24.2	32.1	34.8	42.8	32.7	29.4	44.5	31.4	53.3	40.2
Prior PCI	9.7	13.2	16.6	18.7	19.9	19.5	18.5	14.8	22.0	14.9
Prior CABG	13.2	15.9	21.0	20.3	24.1	22.7	12.3	9.6	9.9	11.7

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails of the overlapping distribution

†Treated at any point during hospitalization or at discharge

Table S.2.11. Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with CABG in Propensity Score Quintiles*: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	45.1	38.6	65.5	68.3	60.9	62.1	75.4	75.7	92.5	93.2
Race Classification										
Forsyth Black	28.9	28.3	13.9	13.1	2.6	3.3	0.0	0.0	0.0	0.0
Forsyth White	4.2	5.2	16.9	16.6	26.4	24.9	41.7	41.6	65.2	68.9
Jackson Black	34.2	30.9	12.5	11.3	2.1	2.1	0.0	0.0	0.0	0.0
Jackson White	4.2	5.4	8.7	8.8	16.7	18.0	11.5	11.0	15.2	13.2
Washington Whites	14.9	15.7	28.8	28.9	20.0	21.1	21.8	21.6	3.2	3.0
Minnesota Whites	13.5	14.6	19.2	21.3	32.3	30.6	25.0	25.9	16.3	14.9
Comorbidities										
Prior MI	32.2	28.6	37.0	43.6	32.3	33.4	30.6	29.2	29.6	27.8
Diabetes	35.8	32.6	24.9	28.3	23.1	22.3	17.3	18.5	19.2	17.5
Never Smoking	47.0	43.3	50.3	49.6	51.4	53.8	57.6	54.3	52.2	55.9
Cardiogenic Shock	2.1	1.4	3.4	5.0	3.8	4.3	3.5	4.2	5.3	4.4
CHF	37.1	35.3	31.9	35.4	29.4	34.2	27.6	24.6	20.6	18.6
Cardiac Arrest	15.9	14.1	12.4	13.2	8.6	12.7	6.4	5.3	3.3	2.1
STEMI	17.1	13.8	19.5	17.7	20.3	21.2	22.0	23.2	21.1	21.1
Study Year										
1987-1991	16.0	13.5	25.5	25.5	25.6	25.0	31.6	29.6	27.3	30.4
1992-1996	12.8	12.5	16.8	15.4	24.4	30.9	25.9	28.5	52.5	48.3
1997-2001	20.3	22.8	27.3	25.6	24.7	23.5	29.5	28.1	20.0	21.1
2002-2008	50.8	51.2	30.4	33.5	25.3	20.6	13.0	13.9	0.2	0.1
Prior PCI	16.6	16.3	15.0	16.7	13.4	10.8	10.1	10.9	8.2	8.2
Prior CABG	22.8	24.7	23.7	25.2	15.2	12.9	4.2	4.4	0.0	0.1

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails of the overlapping distribution

†Treated at any point during hospitalization or at discharge

Table S.2.12. Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with Angioplasty in Propensity Score Quintiles*: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	58.6	61.3	65.6	65.9	66.2	66.0	70.2	69.5	71.8	74.5
Race Classification										
Forsyth Black	13.3	13.2	11.0	10.5	12.0	11.2	9.3	9.9	6.2	5.5
Forsyth White	18.8	20.5	24.8	22.7	29.4	32.3	34.2	32.9	42.7	44.5
Jackson Black	22.3	11.4	13.7	13.1	12.8	11.7	4.5	6.6	0.9	1.8
Jackson White	14.3	17.3	14.4	17.8	9.8	8.1	10.6	8.9	4.4	3.7
Washington Whites	20.5	21.9	20.9	17.9	17.5	18.5	17.9	17.7	9.3	7.8
Minnesota Whites	11.0	15.7	15.2	18.0	18.4	18.2	23.5	23.9	36.6	36.7
Comorbidities										
Prior MI	47.0	50.9	36.5	37.0	28.2	26.1	22.7	20.9	16.9	15.3
Diabetes	31.9	30.4	26.6	29.8	27.9	23.8	23.5	23.9	16.4	16.0
Never Smoking	64.2	65.6	58.4	59.6	49.1	48.6	39.7	38.8	35.5	33.4
Cardiogenic Shock	4.3	6.4	3.9	4.3	3.1	3.6	2.8	2.5	3.6	2.6
CHF	63.9	64.2	34.7	30.0	16.6	16.4	9.5	8.2	1.2	1.5
Cardiac Arrest	15.6	17.8	10.4	8.7	8.1	7.0	5.9	4.8	3.8	5.4
STEMI	7.0	5.9	11.3	11.4	16.9	15.2	24.5	22.1	39.3	47.8
Study Year										
1987-1991	40.6	40.3	31.0	33.7	21.5	22.2	9.8	7.4	4.8	2.5
1992-1996	27.1	27.5	29.0	27.7	29.0	31.9	25.0	25.3	17.1	14.7
1997-2001	18.6	18.4	22.9	23.6	27.1	23.3	30.4	32.2	26.5	26.8
2002-2008	13.7	13.8	17.0	15.0	22.4	22.6	34.8	35.0	51.6	55.9
Prior PCI	6.5	12.1	9.2	13.8	14.4	13.8	17.6	17.5	23.6	20.2
Prior CABG	19.3	25.2	18.1	22.8	14.8	12.8	14.1	12.7	8.5	4.8

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails of the overlapping distribution

†Treated at any point during hospitalization or at discharge

Table S.2.13. Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with IV t-PA in Propensity Score Quintiles*: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	59.1	66.0	66.5	66.5	73.3	72.4	74.0	71.8	73.9	75.6
Race Classification										
Forsyth Black	8.6	11.1	1.9	3.2	2.5	1.9	7.9	7.6	1.6	0.4
Forsyth White	32.7	29.8	36.0	35.7	27.8	32.3	20.5	19.0	31.5	32.5
Jackson Black	16.8	16.7	10.2	8.5	4.8	4.7	6.2	8.4	8.4	5.9
Jackson White	8.7	11.9	12.9	14.4	18.9	13.8	14.4	14.1	14.6	15.4
Washington Whites	10.5	6.8	16.0	10.3	25.9	28.7	39.2	36.7	20.8	24.4
Minnesota Whites	22.7	23.6	23.0	27.9	20.1	18.4	11.8	14.2	23.1	21.3
Comorbidities										
Prior MI	44.8	47.1	29.4	32.1	20.0	14.3	19.8	20.0	11.1	10.1
Diabetes	23.8	19.3	17.8	14.6	9.9	12.6	14.0	13.0	9.7	9.1
Never Smoking	58.2	63.3	55.5	61.4	60.3	60.0	53.3	55.0	56.3	56.1
Cardiogenic Shock	3.6	4.4	3.5	5.7	2.8	3.2	4.1	3.8	6.7	3.8
CHF	40.5	35.3	22.1	22.7	14.2	10.4	17.9	22.1	16.2	12.3
Cardiac Arrest	11.0	13.7	8.4	9.9	7.5	8.9	8.9	9.5	16.4	9.6
STEMI	7.6	4.4	10.1	4.9	13.0	11.0	39.6	50.3	100.0	100.0
Study Year										
1987-1991	32.4	38.0	30.4	39.9	39.0	41.1	32.8	30.0	35.6	35.4
1992-1996	27.3	26.8	30.7	33.8	36.0	32.8	41.8	40.2	41.5	46.3
1997-2001	33.4	31.7	30.0	23.6	17.9	20.4	23.8	27.3	22.9	18.3
2002-2008	6.9	3.6	8.9	2.8	7.1	5.7	1.6	2.5	0.0	0.0
Prior PCI	13.6	13.6	10.5	8.2	8.1	7.0	7.2	8.7	3.3	4.0
Prior CABG	20.0	19.2	10.3	11.3	7.8	5.4	5.9	7.2	2.5	1.8

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails of the overlapping distribution

†Treated at any point during hospitalization or at discharge

Table S.2.14. Distribution of Covariates in Myocardial Infarction Patients Treated and Untreated with Stents in Propensity Score Quintiles*: The Atherosclerosis Risk in Communities Surveillance Study (1987-2008).

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
Variable (%)	Untreated	Treated†	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
Age (mean, SD)										
Male gender	55.2	57.6	63.9	60.5	67.2	63.9	66.5	69.4	76.2	78.5
Race Classification										
Forsyth Black	14.7	18.9	15.7	16.8	13.1	11.1	9.3	7.5	6.4	6.7
Forsyth White	20.0	23.7	24.8	23.3	27.5	28.1	39.1	36.8	33.0	37.5
Jackson Black	32.6	22.2	20.6	22.6	10.7	9.3	3.2	4.8	2.9	3.2
Jackson White	9.2	6.5	8.3	9.1	9.7	8.3	5.8	5.7	2.6	3.8
Washington Whites	13.3	15.0	17.2	15.4	19.0	20.6	16.0	19.6	19.2	13.2
Minnesota Whites	10.2	13.6	13.4	12.9	20.0	22.6	26.6	25.7	36.0	35.5
Comorbidities										
Prior MI	42.4	52.8	31.4	32.8	31.1	25.6	21.0	20.8	16.2	13.9
Diabetes	56.7	55.2	44.0	43.8	30.5	32.9	27.0	23.0	16.5	16.2
Never Smoking	38.4	37.5	31.8	34.2	32.3	28.6	30.6	32.6	32.3	32.6
Cardiogenic Shock	2.3	5.3	3.0	4.1	2.3	1.9	3.0	2.1	2.5	1.9
CHF	74.6	69.7	33.3	26.8	9.1	9.8	3.1	3.8	1.5	1.5
Cardiac Arrest	12.3	12.5	7.0	6.1	4.8	5.0	5.3	4.7	3.2	4.7
STEMI	2.2	2.0	6.6	5.9	7.0	6.5	14.3	15.6	50.0	52.9
Study Year										
1987-1991	---	---	---	---	---	---	---	---	---	---
1992-1996	---	---	---	---	---	---	---	---	---	---
1997-2001	51.9	57.3	49.8	48.6	48.0	47.8	25.5	27.8	27.6	19.7
2002-2008	48.1	42.7	50.2	51.4	52.0	52.2	74.5	72.2	72.4	80.3
Prior PCI	15.6	29.1	16.2	18.8	20.1	16.7	26.6	21.3	17.6	18.8
Prior CABG	24.1	33.5	19.8	20.5	15.9	16.7	15.9	10.0	3.5	4.4

*Quintiles of propensity score distribution from logistic regression models of medical therapy receipt and a standard set of covariates. Non-overlap regions were eliminated and scores were trimmed by 5% on the right and left tails of the overlapping distribution

†Treated at any point during hospitalization or at discharge

Appendix B: Copy of IRB Approval

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

OFFICE OF HUMAN RESEARCH ETHICS
Medical School Building 52
Mason Farm Road
CB #7097
Chapel Hill, NC 27599-7097
(919) 966-3113
Web site: ohre.unc.edu
https://my.research.unc.edu for IRB status
Federalwide Assurance (FWA) #4801

To: Emily Obrien
Epidemiology
137 East Franklin Street Suite 303B Chapel Hill NC 27514

From: Public Health-Nursing IRB

Approval Date: 5/02/2011
Expiration Date of Approval: 4/30/2012

RE: Notice of IRB Approval by Expedited Review (under 45 CFR 46.110)
Submission Type: Initial
Expedited Category: 5.Existing or non-research data
Study #: 11-0908
Study Title: Community Patterns of Acute Myocardial Infarction Therapy and Survival

This submission has been approved by the above IRB for the period indicated. It has been determined that the risk involved in this research is no more than minimal.

Study Description:

Purpose: To estimate the 21 year trends of in hospital use of 6 pharmacological interventions for acute MI including aspirin, beta blockers, calcium channel blockers, IV heparin, ace inhibitors, and statins and 3 revascularization procedures, including fibrinolytic therapy, percutaneous coronary intervention (PCI)and coronary artery bypass grafting (CABG) and survival associated with the use of these therapies. Participants: The study population of interest includes definite or probable MI hospitalizations identified in the Atherosclerosis Risk in Communities Surveillance study from 1987-2007. ARIC surveillance is an ongoing cross sectional study with mortality follow up in 4 U.S. communities. Including criteria are proper age (35-74) and residence with an ICD-9 code consistent with MI. Procedures: Multi variable logistic regression will be used to estimate the association between receipt of each therapy and study year as a number of relevant covariates (gender, sex, age, clinical Comorbidities) to determine trends in medication use over time.

Regulatory and other findings:

This research meets criteria for a waiver of informed consent according to 45 CFR 46.116(d).

Investigator's Responsibilities:

Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

You are required to obtain IRB approval for any changes to any aspect of this study before they can be implemented (use the modification form at ohre.unc.edu/forms). Any unanticipated problem involving risks to subjects or others (including adverse events reportable under UNC-Chapel Hill policy) should be reported to the IRB using the web portal at https://irbis.unc.edu/irb.

Researchers are reminded that additional approvals may be needed from relevant "gatekeepers" to access subjects (e.g., principals, facility directors, healthcare system).

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

CC:
Wayne Rosamond, Epidemiology

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