Long-term Mortality for Older Diabetics Hospitalized with Acute Myocardial Infarction

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Yale University

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LONG-TERM MORTALITY FOR OLDER DIABETICS HOSPITALIZED WITH ACUTE MYOCARDIAL INFARCTION

A Thesis Submitted to the
Yale University School of Medicine and the
School of Epidemiology and Public Health
in Partial Fulfillment of the Requirements for the
Degrees of Doctor of Medicine and Master of Public Health

by
Marwah Abdalla
2006
Abstract

“LONG-TERM MORTALITY FOR OLDER DIABETICS HOSPITALIZED WITH ACUTE MYOCARDIAL INFARCTION”

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Diabetics have higher mortality after myocardial infarction (MI), yet little is known regarding the impact of quality of care on long-term survival in older post-MI diabetics. Using data from the Cooperative Cardiovascular Project (CCP), a national cohort of 234,769 Medicare patients aged 65 or older hospitalized with confirmed AMI between 1994-1995, we assessed differences in 10-year mortality outcomes between diabetics and non-diabetics using Cox proportional regression. To account for quality of care, a composite measure among ideal candidates was constructed and entered into the final model adjusting for use of aspirin & beta-blocker on admission/discharge, angiotensin-converting enzyme inhibitors at discharge, reperfusion within 6 hours of admission, and smoking counseling at discharge. We also assessed the relationship between insulin use, sulfonylureas/biguanides, and statin therapy and long-term mortality within the diabetic cohort.

The final study sample included 203,658 cases: 32% were diabetics. Compared to non-diabetics, diabetics were younger (75 vs. 76, p<0.001), female (53% vs. 47%, p<0.001), had more comorbidities, and unlikely to receive evidence-based care (59% vs. 64%, p<0.001). The unadjusted HR for mortality among diabetics vs. non-diabetics was 1.38 (95% CI: 1.37-1.40). After adjusting for demographics, past medical history, procedures during hospitalization, medications on admission/discharge, and quality of care, the HR was 1.29 (95% CI: 1.27-1.31). Among diabetics, those on insulin or oral hypoglycemic therapy during the initial hospitalization for AMI had the highest risk of mortality during the last 7 years, after adjustment for demographics, clinical characteristics, and quality of care (HR insulin=1.30, 95% CI: 1.25-1.35; HR oral hypoglycemics=1.11, 95% CI: 1.08-1.15) whereas those on statin therapy were not at increased risk (HR statin=0.95, 95% CI: 0.90-1.02).

As compared to non-diabetics, older diabetics had a 29% increase in mortality even after adjusting for demographics, clinical variables during hospitalization, and quality of care (HR=1.29, 95% CI: 1.27-1.31). Additionally, within the diabetic cohort, the risk of long-term mortality was highest among those on insulin or oral hypoglycemic therapy during initial hospitalization for AMI. Our study demonstrates that neither patient characteristics nor quality of care fully account for the poor outcomes among diabetics suggesting that metabolic risk factors associated with diabetes ultimately require therapies beyond those currently recommended for post-MI patients.

Acknowledgements

First and foremost, I would like to thank my family. Throughout all my endeavors, your love, support, guidance, and endless patience have been truly inspirational—“thanks” will never suffice.

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Last, but certainly not least, I am indebted to the patients whose lives and long-term outcomes are represented within this data and to the countless individuals who developed and implemented the Cooperative Cardiovascular Project.
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I. Introduction

Worldwide, cardiovascular disease (CVD) is the leading cause of death (3). The World Health Organization (WHO) estimates that 17 million people die of cardiovascular disease annually, of which 7.2 million deaths are attributable to coronary heart disease (CHD) alone (1). In the U.S., CHD is the leading cause of death (Table 1; Figure 2-3).

In 2002, 1 out of every 5 deaths was attributable to CHD (9). Of those who die of CHD, 83% are over the age of 65 (11). According to the American Heart Association (AHA), in the U.S., acute myocardial infarction (AMI), a subset of CHD caused over 175,000 deaths and led to over $27 billion in healthcare spending in 2002 (9). Additionally, those who have suffered an AMI are more likely to experience sudden cardiac death at a rate 4 to 6 times higher than the general population (9).

<table>
<thead>
<tr>
<th>Diseases and Risk Factors</th>
<th>Total</th>
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<th>Mexican Americans</th>
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<td></td>
<td>71.3 M (34.2%)</td>
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<td>32.4%</td>
<td>41.1%</td>
<td>44.7%</td>
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<tr>
<td>Mortality 2003†</td>
<td>910.6 K</td>
<td>369.2 K</td>
<td>419.2 K</td>
<td>46.0 K</td>
<td>35.8 K</td>
</tr>
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</table>

Table 1: Estimated Prevalence and Mortality from Cardiovascular and Coronary Heart Disease in the U.S. By Race and Gender-Year 2003. Source: “The Atlas of Heart Disease and Stroke” American Heart Association-Modified Table 3 (1)
While traditional risk factors such as smoking, abnormal lipid levels, hypertension, abdominal obesity, and lack of physical activity have long been implicated in the pathophysiology leading to the development of AMI, diabetes is also a strong risk factor for CHD and has even been described by the AHA as a “cardiovascular disease” (12). Worldwide, it is estimated that there are 177 million diabetics and diabetes is now the fifth leading cause of death (13). Currently in the U.S., there are 20.8 million diabetics, of whom 5.2 million also have CHD (Figure 3) (5). While microcomplications such as nephropathy, neuropathy, and retinopathy have long been recognized as causes of increased morbidity and mortality for diabetics, CHD, and in particular AMI, has now become the leading cause of death for diabetics, affecting approximately 55% of patients (14, 15). In fact, of patients hospitalized with AMI, it is estimated that 30% have diabetes (16). Not only are diabetics at a greater risk of developing CHD (17) but once they have cardiovascular complications (i.e. myocardial infarction, congestive heart...
failure (CHF), arrhythmias, or strokes) they have an increased short-term morbidity and mortality.

![Figure 3: Number of Diabetics in Millions (age 35 and older) with Self-Reported Cardiovascular Disease (1997-2003) Source: Centers for Disease Control and Prevention (CDC) (5)]

Unfortunately, the prevalence of diabetes is increasing steadily especially among the elderly (Figure 4; Appendix 1-2) (8). Additionally, as depicted in Figure 5, among diabetics, the elderly also have the highest prevalence of cardiovascular disease. As the population ages the interaction of diabetes and cardiovascular disease will potentially be one of the leading public health problems facing the world and efforts to understand and combat these diseases will be essential.
Although this past decade has been instrumental in characterizing some of the reasons behind the increased morbidity and short-term mortality of diabetics post-MI and while more aggressive secondary prevention efforts have been put in place, diabetics still fare worse during hospitalization for MI as compared with non-diabetics. While much is known about short-term mortality in diabetics post-MI, less is known about long-term...
mortality in this group. Furthermore, little is known about long-term mortality in older patients. Thus, this thesis will characterize long-term outcomes for older diabetics hospitalized with AMI. It is anticipated that results from this study will advance current knowledge about the interaction between diabetes and cardiovascular disease.

*Morbidity and Mortality: Increased Risk after an Acute MI*

One area which has been researched extensively has been the impact of diabetes on the short-term morbidity and mortality associated with AMI (12, 18-23). It has been shown in several studies that after suffering an AMI, diabetics have worse outcomes compared to their non-diabetic counterparts (12, 18-23) although controversy exists whether these worse outcomes are related to the increased comorbid conditions diabetics have. For example, Chyun et al. analyzed the medical records of Connecticut Medicare beneficiaries aged 65 or older who were 30-day survivors of AMI to determine their risk of recurrent MI, CHF, and mortality rates one year post hospital discharge. Results showed that at baseline, compared to non-diabetic patients, diabetics were more likely to have comorbid conditions such as CHF, stroke, chronic renal insufficiency, MI, peripheral vascular disease and hypertension (p<0.001). Analysis of 1-year mortality rates showed that the unadjusted relative risk of death was highest among diabetics, especially non-insulin dependent diabetics (RR=1.55, 95% CI: 1.18-2.03). However after adjusting for comorbid conditions, clinical findings, and myocardial characteristics at time of admission, this no longer remained statistically significant (RR=1.08, 95% CI: 0.82-1.43). In terms of the risk for developing complications, the study showed that the relative risk of readmission for recurrent MI was highest for diabetics. Furthermore, insulin-dependent diabetics were the group most likely to be readmitted for CHF
(RR=2.00, 95% CI: 1.40-2.86) (22). On the other hand, in a retrospective cohort study of 117,599 Medicare patients hospitalized with AMI, Berger et al. showed that diabetic patients had higher 30-day and 1-year mortality rates when compared to non-diabetics after adjusting for differences in comorbidities. Furthermore, among the three different subgroups of diabetics (diet-controlled, on oral agents, on insulin), insulin-treated diabetics had the highest mortality at 30 days and one year even after adjustment for therapeutic interventions, clinical, demographic, and hospital characteristics (OR=1.14, 95% CI: 1.08-1.20 for 30-day mortality; OR=1.48, 95% CI: 1.41-1.55 for 1-year mortality) (24).

Congestive heart failure, along with increased rates of reinfarction and recurrent ischemia, has been noted to be one of the primary causes of the excess in-hospital mortality of diabetic patients post-MI (18, 19). Jaffe et al. found that although diabetic patients had an increased incidence of CHF post-MI, they tended to have smaller infarct sizes when compared to non-diabetics, suggesting that there are other additional factors yet unidentified which may contribute to the excess mortality risk (12, 19, 25-27). Although somewhat controversial, some studies have demonstrated that diabetic patients have more severe coronary atherosclerosis than non-diabetic patients (18, 28-30), suggesting that there are metabolic derangements, such as clotting abnormalities or microvascular disease that place diabetic patients at higher risk of CHD (31). In yet another study, although somewhat controversial, Haffner et al. demonstrated that diabetics without prior MI have similar mortality rates compared to non-diabetics with prior MI even after adjusting for LDL/HDL cholesterol levels, triglycerides, smoking,
and hypertension (HR=1.2, 95% CI: 0.6-2.4) leading the authors to conclude that diabetic patients should be treated as aggressively as non-diabetic patients with prior MI (32).

Whether the increased mortality risk seen in diabetics can be explained by inherent biological differences between diabetics and non-diabetics or whether treatment differences in terms of the quality of care diabetics receive post-MI account for the increased mortality has been extensively debated and is explored in our own study via analysis of the Cooperative Cardiovascular Project (CCP), a national database established to examine quality of care for Medicare patients hospitalized with AMI between 1994-1995. First, however, in order to fully understand the background of this debate and the results from our own study, a review of the biology of AMI in diabetics and the established treatment guidelines for the care of diabetic patients post-MI during 1994-1995 (the time period when initial data for the CCP cohort was collected) is warranted.

Understanding the Pathophysiology of Atherosclerosis and AMI in Diabetics

Traditional risk factors for AMI such as hyperlipidemia, obesity, and hypertension affect diabetics and non-diabetics in a similar fashion. In a follow-up study of the United Kingdom Prospective Diabetes Study (UKPDS), Turner et al. demonstrated that among type 2 diabetics increased low density lipoprotein cholesterol (LDL), decreased high density lipoprotein cholesterol (HDL), hyperglycemia, hypertension, and smoking were all risk factors for coronary artery disease including fatal and non-fatal myocardial infarction (33). Interestingly, the study showed that lipids (increased LDL and decreased HDL) and hypertension were more predictive as risk factors for non-fatal or fatal myocardial infarction rather than hyperglycemia (33). From the results of their study, the authors concluded that type 2 diabetics have similar risk factors for coronary artery
disease as non-diabetics. However, even after controlling for these traditional risk factors, there are additional risk factors which may partially explain the increased risk of cardiovascular disease which diabetes confers on patients. Insulin resistance leading to hyperglycemia, hyperinsulinemia, atherogenic dyslipidemia, and a prothrombotic state are independent risk factors especially in type 2 diabetes that increase the risk of cardiovascular mortality (12, 34). For example, atherogenic dyslipidemia, characterized by three lipoprotein abnormalities—elevated very-low density lipoprotein (VLDL), small dense LDL particles, and low HDL cholesterol, appears frequently in those with insulin resistance. Besides elevated LDL cholesterol, these lipid abnormalities may independently lead to atherosclerosis (12). Additionally, Zareba et al. demonstrated in a study examining 1,045 non-diabetic and diabetic patients post-MI that diabetic patients, especially insulin-dependent diabetics, had higher levels of von Willebrand factor as compared to non-diabetics after adjusting for confounders (35). The authors concluded that endothelial damage is most likely one of the primary mechanisms leading to the increased mortality seen in diabetics post-MI. In fact, it has been shown that diabetics have impaired endothelium-dependent relaxation (18, 36).

In terms of hyperglycemia, results from another UKPDS follow-up study in 2000, revealed that for every 1% decrease in HbA1c levels, the risk for myocardial infarction in diabetics could be reduced by 14% (37). Stevens et al. also used data from the UKPDS to examine differences in risk factors for cardiovascular mortality due to myocardial infarction and stroke (38). They found that those with fatal MIs had higher HbA1c levels, measured within 2 years of diabetes diagnosis, as compared to those with nonfatal MIs suggesting that long-term hyperglycemia impacts mortality rates within a diabetic
cohort. Hyperglycemia, via the presence of advanced glycosylation end products, is theorized to be one of the primary causes underlying this endothelial dysfunction and may lead to an acceleration in atherogenesis (18, 39).

Additionally, in the setting of an acute MI, there are additional abnormalities that place diabetics at increased risk for mortality. Central to the pathophysiology of AMI is platelet aggregation and thrombosis (Figure 6). It is estimated that 90% of AMIs are caused by an acute thrombus overlying an atherosclerotic coronary artery plaque (40). The thrombus leads to further narrowing and complete occlusion of the coronary artery leading to ischemia of the heart muscle (40). When a plaque ruptures, platelets are activated via exposure to the underlying subendothelial collagen triggering the coagulation pathway and thrombus formation (40). Activated platelets also release potent vasoconstrictors such as thromboxane, which contributes to further narrowing of the vessels (40). Because of the metabolic derangements found in diabetes, research has focused on characterizing the pathophysiology of platelet function in diabetics presenting with AMI. In general, diabetics have increased platelet aggregability and an increased procoagulant state as measured by fibrinogen levels and plasminogen activator inhibitor-1 (12, 41, 42). Studies have shown that platelets from diabetic patients produce increased prostaglandins and thromboxane A2 (TXA2) relative to platelets from non-diabetic patients (18, 43). The increased prostaglandins and TXA2 expose fibrinogen binding sites on platelets, leading to the observed increase in platelet aggregation in diabetic patients (44). Activated platelets also appear to be increased in diabetic patients even in the absence of detectable vascular lesions (18). Because diabetics are prone to a more hypercoagulable state, this suggests that they may more easily form thrombi causing
them to experience more severe AMIs and thus have worse outcomes as compared to their non-diabetic counterparts.


**Exploring Differences in Quality of Care: Diabetics and the Elderly**

Besides understanding how biological factors may confer an increased risk of morbidity and mortality in diabetic patients with CHD, other research has centered on identifying whether differences exist between diabetics and non-diabetics in terms of the quality of care they receive. It has been noted that the clinical presentation of diabetics with AMI may differ from that of a non-diabetic, with diabetics having “atypical symptoms” due to autonomic neuropathy leading ultimately to a decreased recognition of AMI (12). Because of impaired angina recognition by both patient and caregiver,
Important intervention therapies may be delayed and morbidity and mortality rates are increased (16).

However, more concerning have been the studies that demonstrate when diabetics suffer AMIs, they are unlikely to receive the same therapeutic interventions as their non-diabetic counterparts (21, 23, 24, 45-48). In a retrospective study of 1,982 Australian patients, Lim et al. examined treatment differences between diabetics and non-diabetics presenting with AMI between 1988-1994. Diabetics were less likely to be prescribed the following therapies on admission: aspirin (76% vs. 85%, p<0.005), beta-blockers (41% vs. 53%, p<0.001), or streptokinase (25% vs. 43%, p<0.001) (23). Similarly, Vaccarino et al. also demonstrated in a larger study examining 160,773 patients aged 30 to 69 hospitalized with AMI between 1994-1998 that diabetics were less likely to receive thrombolytic therapy (18.8/22.7% diabetic women/men vs. 27.6/32.5% non-diabetic women/men), aspirin (74.7/80.5% diabetic women/men vs. 81.2/86.6% non-diabetic women/men), oral beta-blockers (33.0/37.8% diabetic women/men vs. 37.9/42.3% non-diabetic women/men), or alternative reperfusion (9.7/11.7% diabetic women/men vs. 14.0/17.6% non-diabetic women/men) (47). Norhammar et al. in a retrospective analysis of a Swedish registry also investigated treatment differences between diabetics and non-diabetics hospitalized with AMI between 1995-1998. During hospitalization, diabetics were less likely to be treated with heparins (37% vs. 43%, p<0.001), intravenous beta-blockers (29% vs. 33%, p<0.001), thrombolysis (31% vs. 41%, p<0.001) and acute revascularization (4% vs. 5%, p<0.003). Even after adjustment for comorbidities, diabetics were still significantly less likely to be treated with reperfusion therapy (OR=0.83, 95% CI: 0.77-0.89), heparins (OR=0.88, 95% CI: 0.82-0.94), statins
(OR=0.88, 95% CI: 0.80-0.97), or undergo revascularization within 14 days of hospital discharge (OR=0.86, 95% CI: 0.75-0.98) (21).

Using the same database as we did in our present study, Berger et al. analyzed data from the CCP cohort (between January 1994-February 1996) and established that diabetics were statistically less likely to receive aspirin on arrival, beta-blockers on discharge, receive thrombolytics, undergo cardiac catheterization, or coronary angioplasty. Across subgroups of diabetics, patients on insulin therapy consistently received the least appropriate care (24). A major limitation, however, of all the above studies is that contraindications to medical therapy were not accounted for in these analyses. Given the fact that diabetics are known to have more comorbidities, the finding of decreased use of evidence-based therapies may in fact be due to more contraindications to therapy secondary to the increased comorbidities diabetics face.

Both Chowdhury et al. and Krumholz et al. addressed this issue in their respective studies. Like the other authors discussed above, Chowdhury et al. also examined rates of prescription use among a small British cohort of 374 patients between January 1995-December 1995 hospitalized with their first MI. Patients were prospectively evaluated during admission and at one year. At follow-up, diabetic patients were statistically more likely to have evidence of left ventricular failure (47.7% vs. 28.0%, p<0.01). However, the proportion of diabetic patients with left ventricular failure that were prescribed angiotensin-converting enzyme inhibitors (ACE-Is) was less (61% vs. 73.6%, p<0.01). The same pattern was observed for lipid lowering therapy. Although total cholesterol values (>5.5 mmol/L) were significantly higher among diabetic patients at time of 1 year follow-up, they were less likely to be on lipid lowering therapy (27.9% vs. 37.5%,
p<0.05). Although it did not reach statistical significance, the authors also found that the proportion of diabetic patients on beta-blockers and aspirin was lower than for non-diabetics. When closely examined, diabetics had less contraindications to therapy as compared to non-diabetics. The authors concluded that the lower usage of these therapies was not based on contraindications but rather appeared to have little scientific-based justification or explanation (48). Krumholz et al. also adjusted for contraindications to therapy by limiting their cohort to ideal candidates for therapy. From analysis of CCP data from 4 states, Alabama, Connecticut, Iowa, and Wisconsin, non-diabetics were more likely to receive aspirin during hospitalization, aspirin and beta-blocker therapy at discharge, and to undergo cardiac procedures. Using results from a multiple logistic regression model, the authors reported that a history of diabetes was associated with decreased use of aspirin (OR=0.81, 95% CI: 0.70-0.94) and that use of aspirin at discharge was associated with decreased mortality rates 6 months post discharge (OR=0.77, 95% CI: 0.61-0.98) (46).

Like diabetics, evidence exists that elderly patients are also less likely to receive appropriate evidence-based care. Udvarhelyi et al. retrospectively examined differences in processes and outcomes of care post-MI among a Medicare population (n=218,247 patients). The authors found that use of procedures such as angiography, coronary artery bypass graft (CABG), and percutaneous transluminal coronary angioplasty (PTCA) decreased with every 5 year increase in age, after adjustment for comorbidities, suggesting that the most elderly patients are the least likely to undergo procedures as compared to younger patients within the same Medicare population. Other authors have also reported similar findings that suggest elderly patients are less likely to receive
evidence-based care (10, 46, 49-55). Using data from the Worcester Heart Attack Study, a prospective longitudinal study of 9,336 Worcester, Massachusetts residents hospitalized with confirmed AMI between 1975-1997, Jackson et al. examined trends in aspirin utilization and long-term outcomes. The authors demonstrated that over three time periods (1975-1978, 1986-1988, and 1995-1997) diabetics and the elderly were less likely to receive aspirin therapy. They also showed that over a 10-year follow-up period, patients treated with aspirin during initial hospitalization for AMI had increased survival after controlling for study year, patient age, sex, comorbidities, AMI characteristics, and development of heart failure or cardiogenic shock during initial hospitalization (HR=0.85, 95% CI: 0.78-0.92) (56). Given the results from studies like this one, it may be appropriate to conclude that elderly diabetic patients may be the group least likely to receive appropriate care due to the “double bias” against the elderly and diabetics in general.

In an attempt to understand why certain populations such as the elderly and diabetics do not receive appropriate evidence-based care, physician adherence to practice guidelines has been extensively studied and various attempts to improve quality of care have been initiated. One such attempt was the development of the CCP cohort. In 1992, as part of the Health Care Quality Improvement Initiative, the Health Care Financing Administration (HCFA, renamed in 2001 as the Centers for Medicare & Medicaid Services [CMS]) created the CCP. The CCP was designed with the following four objectives:

1) to develop quality indicators describing use of interventions in an ideal group of patients with AMI,
2) to measure the quality of care by relying on these indicators for AMI patients in Alabama, Connecticut, Iowa, and Wisconsin,
3) to use these measurements to direct hospitals to develop quality improvement mechanisms and,
4) to help the HCFA use the CCP as a prototype in the development of similar quality improvement efforts for other conditions besides AMI (53).

Because of its success, the CCP was subsequently nationally expanded and is an ongoing initiative. The CCP is a large well-known cohort that has been validated. Numerous studies have been published over the past decade using data from the CCP that not only have described treatment practices for patients with AMI but also have described changes over time with regards to the quality of care patients hospitalized with AMI have received (10, 22, 24, 51, 52, 55, 57, 58). Likewise, our study will also use data from the CCP to examine quality of care. However, this will be the first time that data on long-term mortality for diabetics will be presented controlling for differences in quality of care. Because our study examines 10-year mortality, it is important to recognize and understand the scientific environment at the time of our study and the potential paradigm shifts in medical practice during this time period especially when interpreting results and formulating conclusions. Thus, a brief history of some of the major controversies during this time period is presented below.

*Practice Guidelines: Management of AMI and Diabetes*

As mentioned above, the CCP was developed in 1992 with four objectives. The first objective was to develop quality indicators describing use of interventions in an ideal group of patients with AMI. In order to achieve this objective, 11 quality of care indicators were developed, based primarily on the 1990 American College of Cardiology (ACC)/American Heart Association (AHA) treatment guidelines for the secondary prevention of AMI. Some of the established guidelines that became the basis for these
quality of care indicators were as follows: use of beta-blockers at admission/discharge, use of aspirin at admission/discharge, use of ACE-Is in patients with low left ventricular ejection fraction (LVEF <40%), avoidance of calcium channel blockers in patients with low left ventricular ejection fraction (LVEF <40%), smoking cessation counseling, use of percutaneous transluminal coronary angioplasty (PTCA) within six hours of onset of chest pain who meet criteria for thrombolysis, use of thrombolytics on admission, administration of heparin, and use of intravenous nitroglycerin for persistent chest pain (53, 59).

Although it was recognized at this time that diabetics had increased mortality post-MI, no separate guidelines for the secondary prevention of AMI existed for diabetic patients during this time period. Thus, specific guidelines for diabetics were only developed after 1995, after our study was initiated (12). Although the 1990 guidelines did not specifically address diabetics, there were prevailing debates within the scientific community about the applicability and the appropriateness of these therapies for diabetic patients that merit discussion and may provide a framework for understanding why diabetics may have been less likely to receive certain medications.

The 1990 ACC/AHA guidelines advised caution with regards to beta-blocker use as secondary prevention in diabetics post-MI. The guidelines stated that one of the relative contraindications to beta-blockade was “difficult to control insulin-dependent diabetes” but did not further specify how this was defined (59). The argument against beta-blocker use in diabetics was the theoretical belief that beta-blockers masked the symptoms of hypoglycemia especially by blunting reflex tachycardia. However, studies showed that there was no significant increase in the incidence of clinically important
hypoglycemic events (60). Likewise, controversy also existed with regards to aspirin therapy. In particular, aspirin was thought to increase the risk of ocular hemorrhages among patients with diabetic retinopathy. Although the results from the Early Treatment Diabetic Retinopathy Study (ETDRS) published in 1992 demonstrated that aspirin did not increase the risk of ocular hemorrhage and that there was a small reduction in cardiovascular events in diabetics (61), the American Diabetes Association (ADA) did not officially recommend aspirin for all diabetics until 1997 (62).

Additionally, one of the major controversies at this time was regarding glucose control and macrovascular complications. In 1993, one year prior to the start of our study, the Diabetes Control and Complications Trial (DCCT) showed that intensive control in type 1 diabetics helped decrease microvascular complications and showed a non-statistically significant trend towards a reduction in macrovascular complications (63, 64). Whether similar intensive glycemic control impacted outcomes for type 2 diabetics was unknown at the start of our study, however there were several ongoing studies addressing this issue at that time. Two of the most important studies were the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study and the United Kingdom Prospective Diabetes Study (UKPDS) — both of which later impacted practice guidelines.

The findings from the DIGAMI study, a randomized controlled trial, were published in 1995 and demonstrated that diabetic patients randomized to an intensive insulin regimen post-MI had decreased in-hospital and 1-year mortality (65). Findings from the 3-year follow-up study published in 1997 also demonstrated that among those that had been randomized to the intensive insulin regimen, an 11% reduction in mortality
3 years post treatment was achieved (63, 66). In 1998, results from a randomized controlled trial (RCT) embedded within the UKPDS\textsuperscript{1} were published. This portion of the UKPDS was designed to determine whether intensive therapy would reduce diabetic microvascular and macrovascular complications. Although it did show an improvement in microvascular outcomes, it only showed a borderline decrease in macrovascular disease (67, 68). Reception of these findings by the scientific and medical community were initially mixed but both studies became landmark articles that impacted practice guidelines especially with regards to the use of insulin and oral hypoglycemics to achieve better glycemic control. Because our study spans the time period when major changes in quality of care and practice guidelines occurred, we will examine long-term mortality outcomes at two time periods: pre- and post-1997/1998. We chose the years 1997/1998 because as discussed above, these were the years that aspirin therapy for diabetics was endorsed by the ADA and the results of the DIGAMI and UKPDS studies were published.

\textbf{II. Statement of Purpose, Specific Aims, and Hypotheses}

The purpose of this study was to examine overall outcomes for older diabetic patients presenting with AMI and to examine the factors associated for the increased mortality risk conferred on diabetics hospitalized with AMI by utilizing a national database, the Cooperative Cardiovascular Project (CCP). Our aims were:

1) To measure and compare 10-year mortality rates for diabetic and non-diabetic patients hospitalized with AMI.

2) To measure compliance rates with established guidelines in place during 1994-1995 regarding cardiac medications as a secondary prevention strategy among diabetic and non-diabetic patients hospitalized with AMI.

\textsuperscript{1} The UKPDS was a 20 year prospective trial that recruited 5,102 patients with type 2 diabetes from 23 clinical centers in England, Scotland, and Northern Ireland.
3) To investigate the role of statin and diabetic therapies (insulin/oral hypoglycemics) in decreasing 3 and 10-year mortality rates for diabetics hospitalized with AMI.

We hypothesize that:

1) 10-year mortality rates for diabetics will be higher as compared to non-diabetic patients before and after adjustment for quality of care indicators.

2) Diabetic patients will be less likely to receive appropriate cardiac medications for secondary prevention.

3) Both statin and diabetic therapies (insulin/oral hypoglycemics) will be associated with decreased long-term mortality rates for diabetics.

III. Methods

Database Source/Selection:

We utilized the Cooperative Cardiovascular Project (CCP), a national database of Medicare patients, (n=234,769) aged 65 or older admitted to non-governmental acute care hospitals in the United States and Puerto Rico. As mentioned previously, the CCP was designed with four objectives: 1) to develop quality indicators describing use of interventions in an ideal group of patients with AMI; 2) to measure the quality of care by relying on these indicators for AMI patients in Alabama, Connecticut, Iowa, and Wisconsin; 3) to use these measurements to direct hospitals to develop quality improvement mechanisms; and 4) to help the HCFA use the CCP as a prototype in the development of similar quality improvement efforts for other conditions besides AMI (53).

Sample Population & Data Collection

All bills submitted by acute care hospitals (UB-92 claims form data) and contained in the Medicare National Claims History File, composed of Part A Medicare
claims, were used to identify discharges (55). The Medicare National Claims History File includes patients treated under fee-for-service plans but does not include bills for those treated under Medicare managed care risk contracts (55). The sample was limited to patients, aged 65 or older, discharged alive with a principal diagnosis of AMI utilizing the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9), code 410.xx. Codes where the fifth digit was a “2” (410.x2) were excluded since this represented an admission for a subsequent episode of care (10). With the exception of five states (Alabama, Connecticut, Iowa, Wisconsin, and Minnesota), patients were identified during an eight-month period using the Medicare National Claims History File. All discharge dates were between February 1994 and July 1995. Because Alabama, Connecticut, Iowa, and Wisconsin were the original four pilot states, hospitalizations were sampled initially between June 1 and December 31, 1992 and then re-measured between August 1 and November 30, 1995 (55). An ongoing study, the Minnesota Clinical Comparison and Assessment Project (MCCAP) caused sampling in that state to be delayed until April-November 1995 (51, 55).

Data Collection:

Medical record abstraction was performed by trained abstractors at two clinical data abstraction centers established by the HCFA (now CMS). Predefined variables were identified from the hospital record and entered directly into a computer database by trained technicians (51). Random re-abstraction of 1,078 pairs of CCP cases was utilized to ensure data reliability. Cases were re-abstracted between March 1, 1995 and November 30, 1995 (7). Variable agreement, as shown in Table 2 below, varied from 91.6% to 98.3% (Kappa, 0.46-0.95) (7, 10, 51). Quality indicator reliability defined as
the agreement rate between two abstractors assessing patient eligibility for a quality indicator and subsequent receipt of the indicator varied from 93.5% to 98.6% (Kappa, 0.41-0.76) as depicted in Table 3 (7, 10).

Table 2: Reliability findings between AMI confirmation and CCP indicators (Modified-Huff et al., Table 3 (7))

<table>
<thead>
<tr>
<th>Quality Indicator</th>
<th>Observation Rate (%)</th>
<th>Agreement (%)</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opportunities to Improve Care (“Ideal” Candidates who did not receive appropriate therapy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy Usage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin during hospitalization</td>
<td>6.9</td>
<td>96.1</td>
<td>0.69</td>
</tr>
<tr>
<td>Aspirin at discharge</td>
<td>5.8</td>
<td>96.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Beta-blockers at discharge</td>
<td>3.5</td>
<td>97.5</td>
<td>0.64</td>
</tr>
<tr>
<td>ACE inhibitor at discharge</td>
<td>3.1</td>
<td>98.6</td>
<td>0.76</td>
</tr>
<tr>
<td>Thrombolysis administered</td>
<td>3.4</td>
<td>95.8</td>
<td>0.41</td>
</tr>
<tr>
<td>Reperfusion given</td>
<td>2.9</td>
<td>93.8</td>
<td>0.53</td>
</tr>
<tr>
<td>Smoking cessation counseling at discharge</td>
<td>6.7</td>
<td>93.5</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Table 3: Reliability findings for CCP composite quality indicators representing opportunities to improve care (Modified-Huff et al., Table 5 (7))

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Observation Rate (%)</th>
<th>Agreement (%)</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI Confirmation</td>
<td>88.5</td>
<td>94.6</td>
<td>0.72</td>
</tr>
<tr>
<td>Therapy Usage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin during hospitalization</td>
<td>77.3</td>
<td>95.6</td>
<td>0.88</td>
</tr>
<tr>
<td>Aspirin at discharge</td>
<td>52.8</td>
<td>94.8</td>
<td>0.90</td>
</tr>
<tr>
<td>Beta-blockers at discharge</td>
<td>32.0</td>
<td>97.4</td>
<td>0.94</td>
</tr>
<tr>
<td>ACE inhibitor at discharge</td>
<td>27.2</td>
<td>98.1</td>
<td>0.95</td>
</tr>
<tr>
<td>Thrombolysis administered</td>
<td>14.0</td>
<td>98.3</td>
<td>0.93</td>
</tr>
<tr>
<td>Reperfusion given</td>
<td>20.8</td>
<td>97.4</td>
<td>0.92</td>
</tr>
<tr>
<td>No calcium blockers at discharge</td>
<td>70.3</td>
<td>97.6</td>
<td>0.94</td>
</tr>
<tr>
<td>Smoking cessation counseling at discharge</td>
<td>9.5</td>
<td>91.6</td>
<td>0.46</td>
</tr>
</tbody>
</table>

AMI and Diabetes Definitions:

The criteria for a confirmed AMI was the following: a discharge diagnosis of an AMI and chart documentation of either a creatine-kinase-muscle-brain isoenzyme (CK-
MB) fraction greater than 0.05 or a lactate dehydrogenase (LDH) level more than 1.5 times normal with a LDH-1 level higher than a LDH-2 level or two of the following three criteria: chest pain, a two-fold elevation of the CK level, or evidence of a new AMI on an electrocardiogram. We did not use troponin levels since they were not widely in use during 1994-1995, hence the necessary data was lacking. The diagnosis of diabetes mellitus was based on chart documentation rather than diagnosis code. We did not use admission serum glucose levels or HbA1c levels as a criterion for the diagnosis of diabetes. We also did not distinguish type 1 diabetes from type 2 diabetes in our subsequent analyses.

**Quality of Care Indicators**

Table 4 lists the quality of care indicator definitions, eligibility, and exclusion criteria used in this study. Quality of care indicators were developed by a steering committee convened by HCFA and the American Medical Association during the pilot phase of the CCP (53). The quality of care indicators were based primarily on the ACC/AHA treatment guidelines for AMI (53). Each indicator had specific criteria to determine potential “eligible” candidates (those who could have received an intervention). This population was subsequently subdivided into two groups: a) ideal candidates—patients for whom treatment should be indicated; and b) less-than-ideal candidates—patients for whom treatment was contraindicated, controversial, or for whom data to determine the appropriateness of treatment was missing (53).
<table>
<thead>
<tr>
<th>Table 4: Quality of Care Indicators-Eligibility and Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin Prescribed During Hospitalization</strong></td>
</tr>
<tr>
<td><strong>Eligible:</strong> All patients with confirmed acute myocardial infarction (AMI)</td>
</tr>
<tr>
<td><strong>Exclusions:</strong> Bleeding on admission, history of peptic ulcer disease or internal bleeding, coagulopathy, chronic liver disease, allergy to aspirin, admission platelet count $&lt;100 \times 10^9/L$, hemoglobin $&lt;10g/dL$, hematocrit $&lt;30%$, serum creatinine $&gt;3mg/dL$, treatment with warfarin on admission, metastatic cancer, or terminal illness</td>
</tr>
<tr>
<td><strong>Criterion:</strong> Received aspirin on day 1 or 2</td>
</tr>
<tr>
<td><strong>Aspirin Prescribed at Discharge</strong></td>
</tr>
<tr>
<td><strong>Eligible:</strong> All patients with confirmed acute myocardial infarction (AMI) discharged alive and eligible for discharge therapies</td>
</tr>
<tr>
<td><strong>Exclusions:</strong> Bleeding on admission or during hospitalization, history of peptic ulcer disease or internal bleeding, acute upper gastrointestinal tract disorder during hospitalization, bleeding, coagulopathy, chronic liver disease, allergy to aspirin, admission platelet count $&lt;100 \times 10^9/L$, hemoglobin $&lt;10g/dL$, hematocrit $&lt;30%$, serum creatinine $&gt;3mg/dL$, treatment with warfarin on discharge, metastatic cancer, or terminal illness</td>
</tr>
<tr>
<td><strong>Criterion:</strong> Aspirin prescription at discharge</td>
</tr>
<tr>
<td><strong>Beta-Blocker Prescribed During Hospitalization</strong></td>
</tr>
<tr>
<td><strong>Eligible:</strong> All patients with confirmed acute myocardial infarction (AMI)</td>
</tr>
<tr>
<td><strong>Exclusions:</strong> Heart rate $&lt;60/min$, systolic blood pressure $&lt;100mm/Hg$, second or third-degree heart block, heart failure, left ventricular ejection fraction $&lt;50%$, bifascicular block, allergy or intolerance to beta-blockers, history of asthma, chronic obstructive pulmonary disease, peripheral vascular disease, shock</td>
</tr>
<tr>
<td><strong>Criterion:</strong> Received beta-blockers on day 1 or 2</td>
</tr>
<tr>
<td><strong>Beta-Blocker Prescribed at Discharge</strong></td>
</tr>
<tr>
<td><strong>Eligible:</strong> All patients with confirmed acute myocardial infarction (AMI) discharged alive and eligible for discharge therapies</td>
</tr>
<tr>
<td><strong>Exclusions:</strong> Heart rate $&lt;50/min$ at discharge (not currently on beta-blocker), systolic blood pressure $&lt;100mm/Hg$ at discharge (not currently on beta-blocker), second or third-degree heart block, heart failure and left ventricular ejection fraction $&lt;50%$, left ventricular ejection fraction $&lt;30%$ or described as severe dysfunction, bifascicular block, allergy or intolerance to beta-blockers, history of asthma, chronic obstructive pulmonary disease, peripheral vascular disease, shock or hypotension during hospitalization</td>
</tr>
<tr>
<td><strong>Criterion:</strong> Beta-blocker prescription at discharge</td>
</tr>
<tr>
<td><strong>Angiotensin-converting enzyme inhibitor (ACE-I) Prescribed at Discharge</strong></td>
</tr>
<tr>
<td><strong>Eligible:</strong> All patients with confirmed acute myocardial infarction (AMI) with left ventricular ejection fraction $&lt;40%$ or described as severe or moderate dysfunction discharged alive and eligible for discharge therapies</td>
</tr>
<tr>
<td><strong>Exclusions:</strong> Aortic stenosis, allergy or intolerance to ACE-Is, systolic blood pressure $&lt;100mmHg$ at discharge (not currently on ACE-I), serum creatinine $&gt;2mg/dL$</td>
</tr>
<tr>
<td><strong>Criterion:</strong> ACE-I prescription at discharge</td>
</tr>
<tr>
<td><strong>Receipt of Primary Percutaneous Transluminal Coronary Angioplasty (PTCA)</strong></td>
</tr>
<tr>
<td><strong>Eligible:</strong> All patients with confirmed acute myocardial infarction (AMI), with ST elevation or left bundle branch block on admission electrocardiogram, and onset of symptoms within 12 hours</td>
</tr>
</tbody>
</table>
Exclusions: Stroke, coagulopathy, bleeding on admission, chronic liver disease, history of internal bleeding or peptic ulcer disease, recent surgery (defined as within the past 2 months), recent cardiopulmonary resuscitation, recent trauma, age >80 years, use of warfarin prior to arrival, evidence that thrombolysis was rejected by patient or physician after initial consideration, cardiac catheterization without angioplasty within 12 hours after admission
Criterion: Receipt of PTCA within 24 hours of admission

**Timing of Thrombolytic Therapy**

Eligible: Same as receipt of PTCA
Exclusions: Same as receipt of PTCA
Criterion: Time from admission to initiation of thrombolytic therapy

**Smoking Cessation Counseling**

Eligible: All patients with confirmed acute myocardial infarction (AMI) discharged alive with cigarette use within year of admission
Exclusions: None
Criterion: Chart documentation of counseling on smoking cessation

Our study sample included 234,769 Medicare patients aged 65 years or older hospitalized with confirmed AMI and who were discharged alive. Only the first AMI admission was included regardless of whether a patient was hospitalized for AMI more than once during the sample period (51). We excluded all transferred patients due to the inability to determine discharge medications. Those who were terminally ill (those with less than 6-month survival as documented in the hospital records), those with “do not resuscitate” (DNR) instructions, or those who had end-stage renal disease were also excluded. After excluding those who were less than 65 years old, had terminal illness, or who were transferred from another hospital, our final study sample was 203,658 patients. For our quality of care analyses, we further restricted the cohort to ideal candidates only, using the specific criteria developed for these indicators as detailed in Table 4.
Demographic & Clinical Variables

Our demographic variables were age, sex, and race. Age was categorized as 65 to 74 years, 75 to 84 years, and 85 years and older. Race was dichotomized as white and nonwhite. Clinical variables for each patient were collected from the medical record and included past medical history, medications on admission/discharge, and in-hospital characteristics and procedures. Comorbidities were obtained from chart documentation and included the following: history of hypertension, stroke, congestive heart failure (CHF), renal dysfunction (serum creatinine >2.5mg/dL or blood urea nitrogen >40 mg/dL), cancer, chronic obstructive pulmonary disease, history of myocardial infarction, previous percutaneous transluminal coronary angioplasty (PTCA), previous coronary artery bypass graft surgery (CABG), dementia, inability to ambulate, albumin level less than 3g/dL, left ventricular ejection fraction (LVEF) less than 0.35, and anemia (hematocrit <30). Smoking status was also obtained as documented in the chart. Admission lab characteristics included respiratory rate greater than 25/min, prothrombin time greater than 16 seconds, pulse greater than 100/min, and evidence of a left bundle branch block on the admission electrocardiogram. In-hospital clinical characteristics and procedures performed included recurrent chest pain, heart failure, stroke, creatine kinase levels more than four times the normal level, PTCA, CABG, and measurement of LVEF. Hospital length of stay was also abstracted. Documentation of medications during admission included aspirin, beta blockers, and thrombolytic therapy. Discharge medications included aspirin, beta blockers, ACE-Is, statins, and bronchodilators. Diabetic medications were identified and abstracted from a file listing all medications used by the cohort and included the following classes of medication: insulin, biguanides,
sulfonylureas, and glucosidase inhibitors. Discharge disposition was coded as home, long-term care, or died. Physician’s specialty was also abstracted based on information listed in the Medicare Part A claims (51). Each physician’s identification number was linked with the HCFA directory of physician-reported specialties (51).

**Outcome Variable**

Our outcome variable was all-cause mortality 3 and 10 years after hospital discharge. Mortality was determined by linking patient data with the Medicare Enrollment Database. The Enrollment Database contains information on all beneficiaries ever enrolled in the Medicare program, including information on dates of death (69). These dates are a compilation of data derived from discharge dates of billing records, which indicate any discharge dispositions of death, and from the Master Beneficiary Record, included as part of Social Security records (52).

**Statistical Analysis:**

Statistical analysis using 2-sided t-tests for differences in means, chi-squared tests for comparison of categorical variables, and Cox proportional regression was used. The data was primarily analyzed according to diabetic status. After testing and confirming graphically that the proportionality assumption for Cox regression was met, a Cox proportional hazards model was used to assess mortality differences. For all mortality analyses time “0” was defined as patient admission to the hospital. We adjusted for potential confounders by including the variables collected as described above: demographics, clinical variables, physician specialty, hospital characteristics, and quality of care indicators. A quality of care composite model was constructed that represented
an opportunity-level composite score (7). Eight quality of care indicators were used to calculate the opportunity and composite score for each patient: aspirin, acute reperfusion, thrombolytics and beta-blocker on admission; aspirin, beta-blocker, ACE-I, and smoking counseling at discharge. A series of Cox proportional hazards models with adjustment for clustering on hospitals were constructed that sequentially adjusted for diabetic status, demographics, clinical and medical history, and finally quality of care. We calculated both unadjusted and adjusted hazard ratios with their respective 95% confidence intervals (CIs). Kaplan-Meier survival curves were plotted and log-rank tests were calculated to determine statistical differences between curves. We also created a diabetic risk-adjusted model to determine the association between prescribed use of insulin, sulfonylureas, biguanides, and statin therapy with 3 and 10-year survival. Similarly, we calculated both unadjusted and adjusted hazard ratios with their respective 95% confidence intervals (CIs). Statistical significance for p-values was set at $\alpha=0.05$. All analyses were performed using STATA 8.00 (STATA Corp, College Station, Tex).

IV. Statement of Student Contribution

This work was a collaboration between many individuals. Both Dr. JoAnne Foody and Dr. Barbara Gulanski provided valuable feedback throughout the thesis process. Dr. JoAnne Foody and Dr. Harlan Krumholz provided access to the CCP database. All statistical analyses were performed by Yun Wang, Ph.D. (Center for Outcomes Research and Evaluation, Yale University). I, along with Drs. Foody and

\[^2\] For example, if a patient was eligible for both aspirin on admission and beta-blocker and ACE-I at discharge, then this patient had three opportunities (denominator). However, if this patient only received two of these therapies (numerator) the overall composite score for this patient would be 0.66.

\[^3\] The statistical command “cluster” specifies observations as independent across groups (clusters) but not necessarily within groups [70]. Stata Corporation. Statistics Data Management Graphics Reference G-0. College Station: Stata Corporation; 1997.
Gulanski, developed the aims, hypotheses, and collectively analyzed the conclusions of this study. All literature searches were performed by this author.

V. Results

Characteristics of the Sample

Diabetics comprised 32% (64,648) of the sample. The demographic and clinical characteristics of diabetic and non-diabetic patients are shown in Table 5 below.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diabetic (N=64,648)</th>
<th>Non-Diabetic (N=139,010)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>75.3 (6.8)</td>
<td>76.5 (7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 65 – 74</td>
<td>36,283 (49.9)</td>
<td>62,110 (44.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 75 – 84</td>
<td>25,606 (39.6)</td>
<td>54,069 (38.9)</td>
<td>0.603</td>
</tr>
<tr>
<td>Female</td>
<td>37,226 (52.9)</td>
<td>64,827 (46.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>55,764 (86.3)</td>
<td>127,958 (92.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical History and Comorbid Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>22,601 (35.0)</td>
<td>39,278 (28.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>5,262 (8.1)</td>
<td>9,563 (6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>9,195 (14.2)</td>
<td>16,175 (11.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of CHF</td>
<td>18,705 (28.9)</td>
<td>23,883 (17.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of CVA</td>
<td>10,893 (16.9)</td>
<td>16,244 (11.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of Chest Pain</td>
<td>18,711 (28.9)</td>
<td>38,573 (27.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46,031 (64.8)</td>
<td>80,149 (57.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>9,427 (13.3)</td>
<td>11,249 (8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>7,000 (10.8)</td>
<td>22,691 (16.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>3,412 (5.3)</td>
<td>8,098 (5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unable to Ambulate</td>
<td>16,266 (25.2)</td>
<td>26,443 (19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt; 2.5 mg/dL or BUN &gt; 40 mg/dL</td>
<td>8,882 (13.7)</td>
<td>10,472 (7.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, mean (SD)</td>
<td>1.5 (1.1)</td>
<td>1.3 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN, mean (SD)</td>
<td>25.5 (14.3)</td>
<td>21.8 (11.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin &lt; 3 g/dL</td>
<td>3,551 (5.5)</td>
<td>5,957 (4.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematocrit &lt; 30</td>
<td>3,729 (5.8)</td>
<td>6,244 (4.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Compared to non-diabetics, diabetics were younger (75 vs. 76, p<0.001). A greater proportion of diabetics were female (53%, p<0.001) and nonwhite (86.3% vs. 92.1%, p<0.001). With regards to medical history and comorbidities, diabetics were more likely to have had a previous MI (35% vs. 28.3%), a history of CHF (28.9% vs. 17.2%) or stroke (16.9% vs. 11.7%), or had previous revascularization procedures, either
PTCA (8.1% vs. 6.9%) or CABG (14.2% vs. 11.6%) (all, p<0.001). On admission, diabetics were almost twice as likely to have renal dysfunction as measured by a serum creatinine greater than 2.5mg/dL or BUN greater than 40mg/dL level (13.7% vs. 7.5%, p<0.001). Diabetics were more likely to present with an admission albumin level less than 3g/dL (5.5% vs. 4.3%), hematocrit less than 30 (5.8% vs. 4.5%), and a prothrombin time greater than 16 seconds (6.0% vs. 5.3%) (all, p<0.001). Diabetics were also more likely to have on admission a left bundle branch block (7.2% vs. 5.4%, p<0.001) and a left ventricular ejection fraction less than 0.35 (18.3% vs. 14.3%, p<0.001), indicating poorer cardiac status. However, diabetics were less likely to have creatine kinase levels greater than 4 times the normal level (28.4% vs. 32.3%, p<0.001).

In terms of hospital procedure and course, diabetics were less likely to undergo PTCA (11.9% vs. 15.7%, p<0.001). Mean length of stay was slightly longer for diabetic patients (7.38 days ± 5.0 vs. 6.82 days ± 4.7, p<0.001). Diabetics were as likely to be discharged home as non-diabetics (61.1% vs. 62.8%, p=0.480). However, those discharged to a long-term care facility were more likely to be diabetic (8.4% vs. 7.8%, p<0.001). Patients who died during initial hospitalization were also more likely to be diabetic (12.2% vs. 10.2%, p<0.001).

**Medications During Admission and at Discharge**

On admission, diabetics were less likely to be prescribed aspirin (83.0% vs. 85.6%, p<0.001), beta blockers (50.3% vs. 56.3%, p<0.001), or thrombolytic therapy (49.8% vs. 63.2%, p<0.001). At discharge, 63% of diabetics were on some form of diabetic medications (26.2% were on insulin therapy and 36.5% were prescribed oral
hypoglycemics, including sulfonylureas/biguanides\textsuperscript{4}: data not shown). Although not the standard of care during 1994-1995, nonetheless, statin therapy was prescribed equally to both diabetics and non-diabetics (4.5% vs. 4.6%, \(p=0.582\))\textsuperscript{5}. As depicted in Figure 7, among ideal candidates at discharge, diabetics were less likely to be prescribed aspirin (63.8% vs. 69.0%, \(p<0.001\)) and beta-blocker therapy (36.3% vs. 42.0%, \(p<0.001\)), whereas they were more likely to be prescribed ACE-Is (60.0% vs. 54.8%, \(p<0.001\)).

![Figure 7: Percent of Diabetic vs. Non-Diabetic Patients Receiving Evidence-Based Medications at Discharge (Among Ideal Candidates)](image)

10-Year Mortality

Our primary analysis revealed a difference in mortality rates between diabetics and non-diabetics throughout the entire 10-year period (Figure 8). In-hospital deaths (i.e. at time of initial hospitalization for AMI) were 12%. Overall mortality for the study sample at 10 years was 69.4%. Compared to non-diabetics, the overall unadjusted 10-year mortality for diabetics was higher (77.2% vs. 65.4%). We constructed multivariate

\textsuperscript{4} The most prescribed sulfonylurea was glipizide. The only prescribed biguanide was metformin. Because of the relatively small numbers of patients on biguanide therapy, we combined sulfonylureas and biguanides in subsequent analyses. Only 1 patient was on glucosidase inhibitors and thus this class of medication was not included in any analyses.

\textsuperscript{5} The most prescribed statin was lovastatin.
models using Cox proportional regression to estimate the overall 10-year mortality risk for diabetics and to adjust for confounders (Table 6). In the unadjusted model we constructed, diabetics had higher 10-year mortality rates as compared to non-diabetics (HR=1.38, 95% CI: 1.37-1.40). After addition of demographic and clinical characteristics to the unadjusted models, the hazard ratio was 1.30 (95% CI: 1.28-1.31). After adjusting for demographics, past medical history, procedures during hospitalization, medications on admission/discharge, and quality of care, the hazard ratio was 1.29 (95% CI, 1.27-1.31).

Figure 8: Differences in Survival Between Diabetics and Non-Diabetics Post-MI (10 Year Data-Unadjusted)

<table>
<thead>
<tr>
<th>Table 6: 10-Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
</tr>
<tr>
<td>Non-diabetics</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
</tr>
<tr>
<td><strong>Adjusted for Demographics &amp; Clinical Variables</strong></td>
</tr>
<tr>
<td>Non-diabetics</td>
</tr>
<tr>
<td>Diabetics</td>
</tr>
<tr>
<td><strong>Adjusted for Demographics, Clinical Variables, &amp; Quality of Care Indicators</strong></td>
</tr>
<tr>
<td>Non-diabetics</td>
</tr>
<tr>
<td>Diabetics</td>
</tr>
</tbody>
</table>
As part of our secondary analyses, we also examined mortality differences between patients who were prescribed statin therapy at discharge and those who were not prescribed statins. The overall 10-year mortality for the statin group was lower compared to those not prescribed statin therapy (54.7% vs. 70.1%). Among the group not prescribed statin therapy, diabetics had a higher mortality rate compared to non-diabetics (77.7% vs. 66.3%). Interestingly as noted above, although there were no statistically significant differences in prescription rates of statin therapy for diabetics vs. non-diabetics (4.5% vs. 4.6%, p<0.001), we found that the overall 10-year mortality rates for diabetics on statin therapy was higher as compared to non-diabetics on statins (67.7% vs. 48.1%, p<0.001; Figure 9).

We further restricted our analysis to diabetic patients only in order to analyze the effect of statin therapy on this cohort. Among diabetic patients those on statin therapy had lower 10-year mortality than those not prescribed statin therapy (67.7% vs. 77.7%, Figure 10).
We conducted further analyses with respect to diabetic related medications. Similarly, diabetic patients on oral medications (sulfonylureas and biguanides) had better 10-year mortality outcomes compared to diabetic patients not on oral hypoglycemics (Figure 11). However, when restricting our analysis to insulin therapy, our Kaplan-Meier survival curves crossed between three and four years post-MI (Figure 12) suggesting non-proportionality. In our subsequent multivariate analysis as depicted below, mortality outcomes between diabetics and non-diabetics were analyzed from admission to three years and from four years to ten years post-MI. Table 7 depicts unadjusted mortality rates for years 1-5 and at 10 years for diabetic patients on insulin and those not on insulin at discharge confirming our Kaplan-Meier findings.
Figure 11: Differences in Survival Between Diabetics on Sulfonylurea/Biguanide Therapy and Diabetics not on Sulfonylurea/Biguanide Therapy Post-MI (10 Year Data-Unadjusted)

Figure 12: Differences in Survival Between Diabetics on Insulin Therapy and Diabetics not on Insulin Therapy Post-MI (10 Year Data-Unadjusted)
### Table 7: Unadjusted Mortality for Diabetic Patients Receiving Insulin therapy Post-MI: Years 1-5 & 10

<table>
<thead>
<tr>
<th>Year Post-MI</th>
<th>On Insulin Therapy</th>
<th>Not On Insulin Therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27%</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>39%</td>
<td>44%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>48%</td>
<td>50%</td>
<td>0.008</td>
</tr>
<tr>
<td>4</td>
<td>57%</td>
<td>56%</td>
<td>0.027</td>
</tr>
<tr>
<td>5</td>
<td>64%</td>
<td>61%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10</td>
<td>80%</td>
<td>77%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Medication Use and Mortality Among Diabetics: Multivariate Analysis

We also constructed a diabetic risk-adjusted model, limiting our analysis to diabetic patients. In particular, we were interested in analyzing the relationship between medication use (insulin, sulfonylureas/biguanides, and statins) and long-term mortality (Table 8). We analyzed the data in two time periods: 1) time from hospital admission to 3 years (includes in-hospital related deaths); and 2) time from year 4-year 10 (excludes in-hospital related deaths). Our choice of these time periods are fully described in the introduction. For this analysis, we adjusted for demographics, clinical characteristics, medications on admission/discharge, and quality of care indicators.

As depicted in Table 8, statin use at both time periods was associated with decreased mortality among diabetics. During the first three years, in the unadjusted model, the hazard ratio for use of statin therapy was 0.58 (95% CI: 0.54-0.62). With full adjustment this protective effect was reduced to 0.73 (95% CI: 0.69-0.78). During the second time period, the unadjusted hazard ratio was 0.90 (95% CI: 0.84-0.95). However, once we adjusted for demographics, clinical characteristics, and quality of care, statin use was no longer associated with a decrease in mortality (HR=0.95, 95% CI: 0.90-1.05). Similarly in our unadjusted models, both insulin use and sulfonylureas/biguanides were
associated with decreased mortality among diabetics during the first three years post-MI (HR for insulin=0.75, 95% CI: 0.73-0.77; HR for sulfonylureas/biguanides=0.55, 95% CI: 0.54-0.57). This association remained even after full adjustment for demographics, clinical characteristics, and quality of care (HR for insulin=0.73, 95% CI: 0.71-0.75; HR for sulfonylureas/biguanides=0.63, 95% CI: 0.62-0.65). However, analysis of our second time period revealed that both insulin and sulfonylureas/biguanides were associated with increased mortality among diabetics during years 4 through 10. In our fully adjusted model, the hazard rate for sulfonylureas/biguanides use was 1.11 (95% CI: 1.08-1.15) while the hazard rate for insulin use was 1.30 (95% CI: 1.25-1.35). Of patients on sulfonylureas/biguanides, 7.9% were also on insulin therapy and thus we observed an interaction between insulin and sulfonylureas/biguanides (data not shown).

<table>
<thead>
<tr>
<th>Model</th>
<th>Years 0-3*</th>
<th></th>
<th>Years 4-10</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>1. Unadjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>0.75</td>
<td>0.73-0.77</td>
<td>1.31</td>
<td>1.26-1.35</td>
</tr>
<tr>
<td>Sulf/Big</td>
<td>0.55</td>
<td>0.54-0.57</td>
<td>1.05</td>
<td>1.02-1.09</td>
</tr>
<tr>
<td>Statins</td>
<td>0.58</td>
<td>0.54-0.62</td>
<td>0.90</td>
<td>0.84-0.95</td>
</tr>
<tr>
<td>2. Adjusted for Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>0.78</td>
<td>0.76-0.80</td>
<td>1.39</td>
<td>1.34-1.44</td>
</tr>
<tr>
<td>Sulf/Big</td>
<td>0.55</td>
<td>0.54-0.57</td>
<td>1.06</td>
<td>1.02-1.09</td>
</tr>
<tr>
<td>Statins</td>
<td>0.66</td>
<td>0.62-0.70</td>
<td>0.98</td>
<td>0.92-1.05</td>
</tr>
<tr>
<td>3. Adjusted for Demographics, Clinical Variables, &amp; Quality of Care</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>0.73</td>
<td>0.71-0.75</td>
<td>1.30</td>
<td>1.25-1.35</td>
</tr>
<tr>
<td>Sulf/Big</td>
<td>0.63</td>
<td>0.62-0.65</td>
<td>1.11</td>
<td>1.08-1.15</td>
</tr>
<tr>
<td>Statins</td>
<td>0.73</td>
<td>0.69-0.78</td>
<td>0.95</td>
<td>0.90-1.02</td>
</tr>
</tbody>
</table>

*Includes in-hospital deaths=12%
Sulf/Big=Sulfonylureas/Biguanides
VI. Discussion

The principal finding of our study is that 10-year mortality for diabetics is higher than for non-diabetics. Our study is unique because we showed that after full adjustment for demographics, clinical variables, and quality of care indicators, diabetics still had a 29% increase in mortality compared to non-diabetics. Our results are consistent with previous studies which demonstrate that diabetics have increased mortality after myocardial infarction (20, 22, 24, 47, 71-73). Our results extend these findings because we had long-term follow-up data and we were also able to adjust for differences in quality of care among the two groups. Our findings suggest that neither patient characteristics nor quality of care fully account for the poor outcomes among diabetics, suggesting that metabolic risk factors associated with diabetes ultimately require therapies beyond those currently recommended for post-MI patients.

The aims of this study were: 1) to measure and compare 10-year mortality rates for diabetic and non-diabetic patients hospitalized with AMI; 2) to measure compliance rates with established guidelines in place during 1994-1995 regarding cardiac medications as a secondary prevention strategy among diabetic and non-diabetic patients hospitalized with AMI; and 3) to investigate the role of statin and diabetic therapies (insulin/oral hypoglycemics) in decreasing 3 and 10-year mortality rates for diabetics hospitalized with AMI. With regards to our aim of measuring compliance rates with established guidelines regarding cardiac medications as a secondary prevention strategy among diabetic and non-diabetic patients hospitalized with AMI, we found that aspirin was not prescribed to 35.5% of diabetics who were ideal candidates for the therapy. Among this group of ideal candidates, beta-blockers were also not prescribed to 63.4% of
diabetics eligible for the therapy. Equally surprising was that overall use of aspirin and beta-blocker therapy at discharge was also low for non-diabetics eligible to receive them. Less than 70% of non-diabetics were prescribed aspirin at discharge and less than 50% of non-diabetics eligible for beta-blockers were prescribed the medication at discharge. Our results are consistent with other studies that have demonstrated that diabetics are less likely to receive evidence-based care post-MI (21, 23, 24, 47, 48, 56). The strength of our study was not only in validating the results of other investigators but we believe our study was able to extend these findings because we limited our analysis to ideal candidates. We believe that our study is valuable for it is in line with the original primary aims of the CCP initiative: to describe quality of care practices among ideal candidates hospitalized with AMI. Our results suggest that there is opportunity for improvement in management of diabetics post-MI since our data confirms that diabetics receive suboptimal medical care.

Underutilization of both aspirin and beta-blockers is surprising since both therapies are a proven and effective secondary prevention strategy for patients post-MI. Additionally, at the start of our study in 1994, ACC/AHA guidelines recommended use of both therapies as secondary prevention strategies for patients post-MI. A meta-analysis of more than 18,000 patients enrolled in randomized controlled trials through March 1990 demonstrated that antiplatelet therapy reduced long-term mortality in both diabetic and non-diabetic patients (74). As noted in the introduction, a possible explanation as to why aspirin and beta-blockers may have been underutilized in diabetic patients is due to the controversies surrounding both therapies at the initiation of our study. The 1990 ACC/AHA guidelines suggested caution when prescribing beta-blocker
therapy for insulin-dependent diabetics most likely due to the theory that hypoglycemic symptoms would be masked as a result of the blunting of reflex tachycardia by beta-blocker therapy. However, this would not explain why non-diabetics were also not receiving this important therapy. With regards to aspirin therapy, although the results of the ETDRS in 1992 showed that aspirin did not increase the risk of ocular hemorrhage, ADA practice guidelines did not recommend aspirin for diabetics until 1997. This may have been due to an additional concern regarding a possible interaction between aspirin and ACE-Is in terms of renal function (75, 76). One study showed that among patients with severe CHF, aspirin therapy attenuated the vasodilator effects of the ACE-I enalapril (77). A subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) demonstrated a negative interaction between enalapril and aspirin and that this interaction was a predictor of mortality (p=0.047). Interestingly, our study showed that among ideal candidates diabetics were more likely to be prescribed ACE-Is as compared to non-diabetics (61% vs. 55% p<0.001). This may suggest that physicians were indeed concerned about a possible adverse interaction between ACE-Is and aspirin and thus chose one therapy over the other. Both Norhammar et al. and Vaccarino et al. in their respective studies also have demonstrated that compared to non-diabetics, diabetics are more likely to be prescribed ACE-Is as opposed to aspirin or beta-blockers (21, 47). However, none of the authors proposed an explanation for this finding. Additionally, unlike our study, their analyses were not restricted to ideal candidates and thus their cohort may have been comprised of diabetics with nephropathy requiring the use of ACE-Is.
While it is important to acknowledge the controversies that existed during the time of our study which may have contributed to the decreased prescription of therapies among diabetics, our findings that among ideal candidates even non-diabetics were receiving suboptimal care suggest that physicians’ adherence to guidelines is less than ideal. As noted previously, evidence exists from several studies that there is underutilization of evidence-based therapies among the elderly in general (10, 46, 49-56, 78-81). Consequently, this was the impetus behind the creation of the CCP. Although great strides have been undertaken to improve quality of care for the elderly and diabetics over the past decade, recent studies show that there are still significant disparities in healthcare especially for diabetics (82, 83). Grant et al. in a retrospective cohort study of 1,765 diabetic patients conducted from 2000-2002 in 30 US academic medical centers demonstrated that physicians did not make appropriate medication adjustments to meet practice guideline goals such as HbA1c levels less than 7%, blood pressure less than 130/80 mmHg, or lipid goals less than 100 mg/dL (84) suggesting that greater improvements are needed in this area.

In order to acknowledge paradigm shifts in medical care that may have unknowingly influenced results from our study, we analyzed our data in two time periods and further restricted our analysis to diabetics only. Unfortunately, because this is a retrospective study, it is difficult to determine with certainty to what extent if any our data is subject to a period effect. We were concerned given the controversies that existed with regards to medical therapy that there were systematic differences between groups that would have influenced our data. For example, because of the national scope of our data, academic centers, where many of these landmark studies originated, may have
treated diabetics more aggressively even before practice guidelines officially changed as opposed to community hospitals. We tried to limit this by controlling for hospital characteristics and adjusting for clustering among hospitals but there may be additional unknown confounders for which we did not adjust. We did not apply further regression techniques to explore this issue and is a limitation of our study.

Surprisingly, the analysis of our data in two time periods revealed an interesting relationship between insulin therapy and mortality within the diabetic cohort. Within the first three years, in our fully adjusted model, insulin therapy was associated with decreased mortality (HR=0.73, 95% CI: 0.71-0.75) whereas in the remaining seven years, it was associated with increased mortality (HR=1.30, 95% CI: 1.25-1.35). The same was true for sulfonylurea/biguanide therapy (HR years 0-3=0.63, 95% CI: 0.62-0.65; HR years 4-10=1.11, 95% CI: 0.71-0.75). Berger et al. also found an increased risk of mortality with insulin use while a study by Chyun et al. did not find this association (22, 24). It is important to note that both authors used data from the CCP but only analyzed short-term mortality. The study by Berger et al. was national in scope whereas the study by Chyun et al. was limited to Connecticut. Although our data revealed an increase in mortality after the third year while Berger et al. found this association at one year, we agree with the conclusions of Berger et al. and believe this most likely represents confounding and that this association represents increasing disease burden among diabetics as time progresses. In other words, insulin may just be a marker of disease progression. We cannot draw any firm conclusions because we did not have information on medication dosages so we cannot fully correlate medication with outcomes. We cannot determine if those who reaped a benefit in the first three years were on high or
low dosages of insulin, whether they had just been started on therapy during initial hospitalization for AMI, or what their admission glucose levels/HbA1c were. It is known that stress hyperglycemia at the time of initial MI can increase the risk of death. A recent meta-analysis described that non-diabetics who had glucose concentrations between 6.1-8.0 mmol/L had a 3.9 increased risk of mortality (95% CI: 2.9-5.4) as compared to non-diabetics with lower glucose concentrations. Higher range of glucose concentrations (8.0-10.0 mmol/L) increased the risk of CHF or cardiogenic shock. Among diabetic patients those with glucose concentrations between 10-11.0 mmol/L had a 1.7 increased risk of mortality (95% CI: 1.2-2.4) (85).

An alternative, but admittedly less likely explanation for our finding is that this may represent “metabolic memory” similar to the recent findings of the Epidemiology of Diabetes Intervention and Complications (EDIC) study, an 11-year follow-up of DCCT participants. The EDIC study showed that CVD events were reduced years after intensive insulin therapy among type 1 diabetics had ended in the original randomized controlled trial (86). However, unlike our study this was a randomized controlled trial in type 1 diabetics who had undergone years of intensive insulin therapy. It is highly unlikely that patients received an intensive insulin regimen during hospitalization and if they did, as mentioned previously, we do not have information regarding medication dosages to determine the effect. Additionally, we do not have information regarding type of diabetes or duration of disease. Thus, without information regarding type of diabetes, duration of disease, medication dosages, and glycemic-related admission characteristics, we cannot analyze this finding further or make any firm conclusions. How intensive insulin therapy affects CVD and long-term outcomes will most likely be answered by
several ongoing randomized controlled trials such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, results for which are expected in 2009.

Similarly our findings for sulfonylureas are difficult to interpret. We were surprised to find that while our unadjusted Kaplan-Meier curve did not indicate a cross-over in mortality between years 3 and 4, our Cox regression models did. As indicated previously, a proportion of patients on sulfonylureas were also on insulin therapy. Our findings most likely suggest an interaction between these therapies, however we were not able to evaluate this further and is a limitation of our study. Additionally, there has been conflicting information regarding the effect of sulfonylureas and CVD mortality. Because sulfonylureas close potassium channels, it has been hypothesized that closure of these channels in cardiac cells impairs ischemic preconditioning, which normally allows cardiac cells to survive during periods of ischemia (87). Another theory is that sulfonylurea toxicity is pro-arrhythmic (87). The University Group Diabetes Project (UGDP) study demonstrated that those treated with the sulfonylurea agent, tolbutamide, had higher cardiovascular-related deaths than those on placebo whereas results from the UKPDS showed that sulfonylurea therapy with glyburide did not increase risk of death (88, 89). A recent meta-analysis demonstrated that a dose-response relationship exists among first generation sulfonylureas and glyburide therapy and mortality among type 2 diabetics (87). It should be noted that in our study the most prescribed sulfonylurea was glipizide which was not specifically studied in this meta-analysis but both glyburide and tolbutamide were also used by patients in our cohort. Again, because we did not abstract
information on medication dosages, we cannot adequately evaluate the relationship between sulfonylureas and mortality.

In contrast, we demonstrated that statin therapy was mostly associated with decreased mortality over the 10-year time period (HR years 0-3 fully adjusted model=0.73, 95% CI: 0.69-0.78; HR years 4-10 fully adjusted model=0.95, 95% CI: 0.90-1.02). Statin therapy is now the mainstay of cardiac therapy and thus it is not surprising that as numerous studies such as the Scandinavian Simvastatin Survival Study Group (4S), the Cholesterol and Recurrent Events (CARE) trial, and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group have demonstrated, statin therapy decreases mortality even among diabetics (90-93).

**Strengths and Limitations**

Our study was subject to several limitations. First, because this is a retrospective study it is subject to limitations inherent to such a design. The data used in this study is only reflective of what was documented in patients’ charts. Certain therapies may not have been recorded. Errors in medical abstraction could have also occurred, especially in the identification of ideal candidates, leading to misclassification. This misclassification is most likely non-differential and would bias our results toward the null. Medical record abstraction is difficult because charts may sometimes be illegible, poorly organized, and because charts are written as narratives rather than standardized forms, the ability to abstract the necessary data may be challenging (10, 55). Although validation studies of the CCP have documented high reliability of the data abstracted (7), the data is not perfect. Lastly, because we excluded transferred patients we may have introduced a selection bias.
As compared to randomized controlled trials, observational studies are often subject to uncontrolled confounding. Because we only abstracted clinical data regarding cardiac and diabetic medications we cannot account for use of other medications either physician prescribed or over-the-counter medications (i.e. vitamins), that may have affected our analysis. For example, we do not have information on the percentage of women in the cohort who may have been taking hormone replacement therapy (HRT) which at the time of our study was thought to decrease the risk of coronary events (94). This is an important confounder because after the initiation of our study, results from the Women’s Health Initiative in 2003 showed that HRT increases cardiovascular-related mortality (95). Other important confounders to consider are socioeconomic status, education, and lifestyle characteristics such as exercise, including cardiac rehabilitation post-MI, and diet.

Most importantly, the CCP was not originally designed to assess diabetic outcomes. As mentioned previously, we did not distinguish between the different types of diabetes in our sample. Also, we did not have information regarding duration of disease or several important admission characteristics such as body mass index, glycemic variables (i.e. HbA1c levels or fasting plasma glucose levels), lipid levels, or medication dosages. Because diabetic status was not confirmed via measurement of HbA1c levels or fasting plasma glucose levels, we may have underestimated the prevalence of diabetes, potentially resulting in disease misclassification. Again, this most likely represents non-differential disease misclassification biasing our results towards the null. It should be noted that statin therapy was not part of the standard of care during this time period and no quality of care indicators were developed for this therapy. We were unable to
correlate cholesterol levels on admission with statin therapy and we could not reliably
determine what the independent effect of statin use in this cohort had on long-term
mortality. However, although it was not the standard of care during this time period,
statin therapy was prescribed equally to both diabetics and non-diabetics (4.5% vs. 4.6%,
p=0.582). Furthermore, among those treated with evidence-based therapies, we do not
know whether patients were treated to target levels so we cannot reliably determine the
effect this had on mortality. With regards to our primary outcome, mortality, we did not
analyze cardiovascular-related mortality but rather all-cause mortality. Lastly, practice
guidelines for the care of patients with AMI along with diabetic management have
changed considerably. Thus, caution should be employed when trying to generalize these
findings to a contemporary cohort.

Although we acknowledge these limitations, we believe our study has several
strengths. The CCP is a well-known, large cohort that has been validated and provides a
comprehensive picture of the quality of care of elderly patients hospitalized with AMI.
Numerous published studies have used data from the CCP to describe treatment practices
for patients with AMI and describe changes over time with regards to the quality of care
patients hospitalized with AMI have received (10, 22, 24, 47, 51, 52, 55, 57). However,
data regarding diabetic patients in this cohort have been minimal especially with regards
to long-term follow-up. This is the first time that 10-year mortality data from the CCP
cohort looking at diabetic mortality has been presented. We limited our mortality
analysis to patients who were ideal candidates for these therapies. Therefore, we were
able to examine the impact quality of care had on long-term mortality outcomes.

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6 We presented an abstract of some of our initial findings at both the ADA Scientific Sessions (San Diego,
California, June 2005) and the AHA Scientific Sessions (Dallas, Texas, November 2005).
Because the CCP utilizes cases from the Medicare databases, we were able to decrease selection bias that may result from randomized trials. Use of Medicare data also eliminates the ability to pay for care as a confounder in our study. While we recognize practice guidelines have changed considerably, it has also been noted that practice guidelines are slow to disseminate and thus the patterns we observed in our study with regards to treatment and procedure use may in fact be reflective of care patients received several years post 1994-1995 (81, 96, 97).

**Conclusion**

The impetus behind this thesis was to determine reasons behind the observed increased mortality diabetics face post-MI and to determine how quality of care impacts long-term outcomes for this group. As discussed, several authors have attempted to characterize whether this increased short-term mortality is due to biological differences or whether this increased mortality is due to health disparities—namely a difference in the quality of care diabetics receive post-MI. Additionally, few studies have specifically examined long-term mortality for diabetics post-MI. Our findings that both non-diabetics and diabetics were less likely to receive evidence-based therapies post-MI suggest that we need to encourage physicians to adopt and better implement evidence-based guidelines especially for those historically most vulnerable to disparities in healthcare: the elderly and diabetics. As the number of diabetics increase worldwide and as the population ages, elderly diabetics will be the group most in need of new and effective strategies in order to successfully combat their diseases and decrease their mortality. As recently demonstrated by Eagle et al., the implementation of guideline-based AMI standard care is associated with improved 30-day and 1-year mortality within a Medicare
cohort post-MI (98). By extension, we believe that implementing guideline-based AMI standard care can likely improve long-term outcomes as well. However, our findings also suggest that even after accounting for quality of care, diabetics still have a substantial increase in long-term mortality. While our study is one of the first to highlight long-term mortality outcomes for elderly diabetics, more research is clearly needed in this field. For example, future studies examining sex-based differences with regards to long-term mortality for elderly diabetics will be valuable. Studies also examining cardiovascular-related mortality will be extremely informative. We believe that in order for this research to be successful, it will require a collaboration between basic scientists, clinicians, and epidemiologists to identify and address both the underlying metabolic factors and disparities in quality of care that clearly place elderly diabetics at greatest risk of mortality post-MI.
A2. Estimated Prevalence of Diabetes by Age Group (Developed vs. Developing Countries): Year 2000 and 2030. Source: World Health Organization (2)

A3. Incidence of Myocardial Infarction in Diabetics and Non-Diabetics with and without prior MI. Source: “Diabetes and Cardiovascular Disease: Time to Act” International Diabetes Federation (6)
VIII. References


84. Grant RW, Buse JB, Meigs JB, for the University HealthSystem Consortium Diabetes Benchmarking Project Team. Quality of Diabetes Care in U.S. Academic Medical Centers: Low rates of medical regimen change Diabetes Care 2005;28(2):337-442.