Published in final edited form as:
Am J Cardiol. 2009 August 15; 104(4): 492–497. doi:10.1016/j.amjcard.2009.04.007.

Usefulness of Diabetes Mellitus to Predict Long-term Outcomes in Patients with Unstable Angina Pectoris

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Abstract

The objective is to determine short and long-term cardiovascular (CV) outcomes in unselected diabetic patients with acute ischemic chest pain (AICP). For diabetic patients presenting to the emergency department with AICP, the short-term CV outcomes remain discordant between trials and registries, whereas the long-term outcomes are not well-described. A consecutive cohort of all residents of Olmsted County, Minnesota, presenting with AICP during the period January 1, 1985 through December 31, 1992 were followed for a median duration of 16.6 years. The primary outcome was long-term all-cause mortality. Other outcomes included a composite of death, MI, stroke, and revascularization (MACCE); and heart failure (HF) events at 30 days and a median of 7.3 years respectively. Of the 2271 eligible patients, 336 (14.8%) were classified with diabetes mellitus (DM). The crude 30-day MACCE rate was 10.1% in diabetic patients and 6.1% in non-diabetic patients (p=0.007). HF events were more common in diabetic patients at 30 days (9.8%, vs.3.1%, p<0.001). At 7.3 years, diabetic patients were more likely to experience MACCE and HF events than non-diabetic patients (71.2% vs. 45.1%, unadjusted HR 2.15, 95 % CI 1.87-2.48, p<0.001) and (45.1%, vs. 18.2%, p<0.001) respectively. Over the follow-up period, 272 (81.9%) diabetic patients died compared to 936 (49.2%) non-diabetic patients (p<0.001). In conclusion, DM is associated with a higher short-term risk of MACCE and HF and a higher long-term risk of mortality in unselected patients with AICP. DM should be included as a high-risk variable in national acute coronary syndrome guidelines.

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Disclosures: The authors have no conflict of interests to disclose.

Keywords

Diabetes; Outcomes; ACS; Chest Pain; Guidelines

In long-term follow-up, data from a pooled analysis of TIMI trials demonstrated that diabetes mellitus (DM) was associated with a higher mortality at 1 year than patients without DM 1. This increased risk of death was also observed in a large international registry at 2-years which also documented a higher risk of subsequent heart failure (HF) 2. The longest follow up of mortality for diabetic patients with non ST elevation acute coronary syndrome (NSTE ACS) is 4 years 3. Despite this evidence, and the recognition that DM is one of the most important risk variables in the causation of coronary heart disease (CHD), DM is currently not included as an independent high-risk variable in the national and international risk assessment guidelines for patients presenting with suspected ACS 4, 5. We present findings from a unique community-based cohort of consecutive NSTE ACS patients, with and without DM, who were followed for more than 15 years.

Methods

Using written screening logs, we retrospectively identified all residents of Olmsted County, Minnesota (OC) presenting to one of the County's three emergency rooms with acute chest pain during the period January 1, 1985 through December 31, 1992. The complete medical records of all County residents presenting with their first episode of acute chest pain, consistent with an unstable coronary syndrome, in during the study period were reviewed by an experienced nurse abstractor. This was defined according to the Diamond classification as follows: new onset or worsening pattern of ischemic chest pain, occurring at rest or with minimal exertion, and alleviated by sublingual nitroglycerin and/or rest 6.

Patients were excluded if they had an electrocardiogram suggestive of ST segment elevation myocardial infarction (STEMI), or a definitive alternate etiology for the chest pain, including pulmonary embolism, pneumonia, musculoskeletal pain, pericarditis and dissecting aortic aneurysm. Diabetic patients were identified from notations in the medical record that included a recorded diagnosis in the past medical history and use of anti-hyperglycemic medication. Both patients with type 1 and type 2 DM were included.

For all eligible patients, the complete medical record was abstracted to determine the history of the qualifying episode, including detailed physical examination findings, as well as past medical history. This was carried out through the resources of the Rochester Epidemiology Project 7. The qualifying electrocardiogram was interpreted by a staff cardiologist from the Mayo Clinic and verified by one of the study physicians. Using the Agency for Health Care Policy and Research (AHCPR) criteria, which form the basis for chest pain clinical risk stratification in the current American College of Cardiology/American Heart Association guideline 4, 8, patients were classified into high-, intermediate-, and low-risk categories. Patients subsequently ruling-in for myocardial infarction, with a CK-MB or CK level greater than twice the upper limit of normal anytime within the first 24-hours of ED presentation, were classified as the evolving myocardial infarction group. Troponins were not available during the study period.

Long-term data were collected in two phases. In the first phase, major cardiovascular (CV) adverse events and cerebrovascular events (MACCE) including death, MI, stroke and need for revascularization were measured. Study subjects who did not have ongoing medical care visits in OC were contacted to determine vital status. The first phase of long-term patient follow-up ended September 29, 1998.

In the second phase, last known alive dates or death dates as of January 2007 were added. Death dates were obtained through the State of Minnesota and OC death records. Thirty-seven patients were excluded at this time for refusal to allow use of their records for research purposes.

Continuous data are presented as mean and range and compared between diabetics and non-diabetics with Student's t-test. Categorical data are summarized as frequency (percentage) and compared with Pearson's chi-squared test. Survival rates are estimated using Kaplan-Meier (KM) methods and compared with the log-rank test. Logistic regression models were used to estimate unadjusted and partial (adjusted) odds ratios between DM and other risk factors and 30 day events. Cox proportional hazards models were used to estimate the marginal and partial effects of DM and other risk factors on follow-up mortality and MACCE. Interactions between age and DM and gender and DM were investigated and retained if statistically significant and omitted if not. Covariate risk factors were included if they had significant unadjusted associations with the endpoint. No variable selection was done except for the aforementioned testing for interactions.

Results

There were 6,801 residents of OC who presented to an emergency room with their first episode of acute chest pain during the study period, January 1, 1985 through December 31, 1992. Of these, 2,271 (33.4%) met eligibility criteria for NSTE ACS and were followed as study subjects for a median of 7.3 years for MACCE. Of the ineligible patients, cardiac causes accounted for 6.7% of patients including STEMI in 5.5%, stable angina in 1.0% and aortic dissection in 0.2%. Non-cardiac causes of chest pain accounted for 36.2% of patients, 23.9% of patients were excluded because of an indeterminate cause, 17.6% because they were non-residents, and 15.6% for other reasons. After extending the follow-up data for vital status, 2234 study subjects were followed for a median of 16.6 years.

Of the 2271 patients, 336 (14.8%) patients had previously diagnosed DM. Table 1 lists the baseline characteristics in diabetic patients compared to non-diabetic patients. Diabetic patients were older, more likely to have had an MI, or NSTE ACS, or chronic stable angina. Diabetic patients were also more likely to have hypertension, use aspirin, and have an electrocardiogram abnormality. However, they were less likely to be smokers.

In unadjusted analysis, diabetic patients were more likely to suffer a MACCE in the short-term (Table 2). At 30 days, 14 (4.2%) diabetic patients versus 43 (2.2%) non-diabetic patients (p=0.035) had died and were also more likely to suffer a stroke. No stroke events were related to percutaneous coronary intervention (PCI). Thirty-three diabetic patients had heart failure (HF) at 30 days (9.8%) versus 60 non-diabetic patients (3.1%, p <0.001) at 30 days, with HF defined as a clinical diagnosis based on symptoms of dyspnea on exertion, orthopnea and fatigue. In multivariate modeling, diabetes was no longer associated with 30-day MACCE (OR 1.72; 95% CI 1.15-2.56; p=0.008). However, diabetes remained associated with HF after controlling for age, prior MI, prior unstable angina, prior stable angina, hypertension, an abnormal index electrocardiogram, and left bundle branch block (OR 2.42; 95% CI 1.52-3.85; p<.001).

Diabetic patients were at greater risk (unadjusted HR 2.15; 95% CI 1.87-2.48; p<0.001) for MACCE on long-term follow-up (Figure 1). At seven years of follow-up, there were 227 MACCE among diabetic patients (71%; 95% CI 66-76%) and 779 MACCE in non-diabetic patients (45%; 95% CI 43-48%, Table 3). In a multivariable model, the significant association between DM and long-term MACCE persisted (Table 4). There was a significant interaction (p=0.032) between age and DM such that the effect of DM on long-term

MACCE was more pronounced in younger patients (HR 3.19; 95% CI 1.65-6.18, age<50 years) than in older patients (HR 0.80; 95% CI 0.45-1.41, age≥90 years). In addition, the adverse effect of DM on MACCE was more pronounced in women. This gender effect was not secondary to differences in the rates of revascularization. At 7.3 years, diabetic patients were also significantly more likely to suffer with HF (121 events, 45.1%, vs. 285 events, 18.2%, p<0.001).

In multivariable analysis, DM was not associated with a significant effect on 30-day mortality (OR 1.43; 95% CI 0.75-2.72; p=0.28). In multivariable analysis, after controlling for age, prior MI, stable angina, hypertension, abnormal electrocardiogram, systolic blood pressure, and index MI, DM was not associated with a significant effect on 30-day mortality (OR 1.28, CI 0.85-1.95, p=0.24). At intermediate and long-term follow up, DM adversely impacted survival. The median survival among diabetic patients (Figure 2) was 7.5 years compared with 16.5 years among non-diabetic patients (HR 2.45; 95% CI 2.14-2.81; p<0.001). At the end of follow-up, 272 (81.9%) diabetic patients compared to 936 (49.2%) non-diabetic patients had died (p<0.001). In a multivariable model, DM was associated with a significant increase in long-term mortality, with different effect depending on age (Table 5). Similar to the model results for MACCE, this effect was less pronounced in older patients compared with patients <50 years old, in whom there was a strong association with follow-up mortality (HR 4.70; 95% CI 1.56-14.1; p=0.006), which decreased with increasing age. In patients 90 years and older, the association was not significant (HR 1.08; 95% 0.71-1.63; p=0.73).

In an unadjusted comparison of diabetic patients with low-to-moderate AHCPR risk and non-diabetic patients with high AHCPR risk, survival was similar for the first 8 years (Figure 3). A divergence in the KM curve after this time resulted in a significant difference between the two groups (HR 1.29; 95% CI 1.07-1.56; p=0.009) with low-to-moderate risk diabetic patients fairing worse than non-diabetic high risk patients. Diabetic patients with high AHCPR criteria performed consistently worse than both groups.

Discussion

Cardiovascular outcomes in diabetic patients presenting with ACS have been described in data from trials and registries 1-3, 9-12, have focused primarily on short-term outcomes and reported conflicting results. Diabetic patients with ACS managed invasively have also demonstrated higher rates of composite ischemia and major bleeding, as evidenced by an analysis from the ACUITY trial 13. Our study is unique in that it consists of a large, consecutive, community-based cohort of patients with both short- and long-term follow up, and is largely free of selection bias.

On short-term follow up at 30 days, we found that unselected diabetic patients presenting with AICP had a higher crude rate of death and stroke. The baseline characteristics and short-term findings from large ACS registries are similar to our study, suggesting that registry data provide a good representation of day-to-day practice and outcomes. In-hospital data from the OASIS registry reveal a higher crude rate of death and stroke in diabetic patients, without any increase in MI 1. The GRACE registry reported that younger diabetic patients and those on insulin were more likely to die 10. The Euro Heart Survey of ACS demonstrated increased in-hospital mortality in diabetic women, but not in diabetic men 11. This variable effect of gender on short-term mortality and MACCE was not observed in our cohort.

In a multivariate model, the 30-day data from our cohort of diabetic patients did not demonstrate an independent effect of DM on MACCE. However, multivariate analysis in

diabetic patients can potentially underestimate the inherent CV risk posed by DM. This is likely the result of unintended statistical over-adjustment for variables such as hypertension, obesity, prior revascularization, chronic kidney disease, and other co-morbidities, present more frequently in diabetic patients. The higher risk of stroke in our cohort of diabetic patients in the short-term may be explained by the higher coexisting rates of hypertension, coronary bypass, and extensive atherosclerosis. Unlike our study, multivariable-adjusted pooled trial data from 11 TIMI studies revealed that diabetic patients with ACS had a higher risk of death at 30 days 3. This difference may be explained by the preferential enrollment of higher-risk populations in the constituent TIMI trials.

The higher incidence of new-onset HF at 30 days in diabetic patients in our study has been previously observed in the GRACE and OASIS registries 1, 10. This excess risk of HF in diabetic patients has been postulated to result from disturbances in microvascular circulation, abnormalities in myocardial glucose and free fatty acid metabolism and by hyperglycemia-induced myocyte necrosis, apoptosis, and fibrosis 14.

Longer-term follow up data in unselected diabetic patients presenting with an index episode of ACS are non-existent. Our study is unique in that it provides long-term follow up, to a median of 7.3 years for MACCE and 16.6 years for mortality in diabetic patients with NSTE ACS. The longest previous follow up of 4 years in 170 diabetic patients with ACS from the PRAIS-UK registry failed to find a significant independent effect of DM on mortality. Pooled data from five TIMI studies did not reveal DM to be an independent predictor of death at 1 year 12. The heterogeneous and generally higher-risk studies pooled for analysis limits their generalizability. However, 2-year findings of the unselected OASIS registry showed that DM was associated with a significantly higher mortality, similar to our study.

It was also evident from our analysis that the adverse CV effect of DM was most pronounced in younger patients. The absence of an independently adverse CV effect of DM in patients older than 90 is likely to have resulted from a higher burden of co-morbid CV conditions. The increased long-term MACCE rate associated with DM in women in the long-term are consistent with findings from the OASIS registry 1. Also critically important was the diabetic patients' prognosis, comparable to non-diabetic patients classified at high-risk by AHCPR criteria. These data emphasize the need for aggressive risk assessment and management in diabetic patients, institution of evidence-based therapies, and development of diabetes-specific treatments that can ameliorate accelerated atherosclerosis and exaggerated thrombosis.

We acknowledge some limitations in our study. The diagnosis of DM was based on review of medical records. Information about the duration and control of DM, baseline LV function, prior history of heart failure, and renal function was unavailable. Since data was collected retrospectively, undiagnosed diabetic patients may have been misclassified at the outset. This misclassification likely resulted in an overestimation of MACCE rates in non-diabetic patients. In addition, no data was available on patients who may have developed DM during the course of the long follow up. It can be argued that the demographic and patient compliance patterns in OC are not entirely representative of epidemiologic and disease patterns in other parts of the US. Although this is well-recognized, evidence from international studies argues against perceived differences in the impact of risk factors for CHD between different racial and cultural groups 15, 16 Another important limitation to our study is the lack of data on treatment modalities in diabetic patients, as it has been well reported that evidence-based therapies remain underutilized in diabetic patients with acute coronary syndromes 17, 18. Finally, the lack of troponin assay at the time of the study likely underestimated the proportion of patients with NSTE-MI.

Acknowledgments

Supported by NIH Grant AR30582-43, The Rochester Epidemiology Project.

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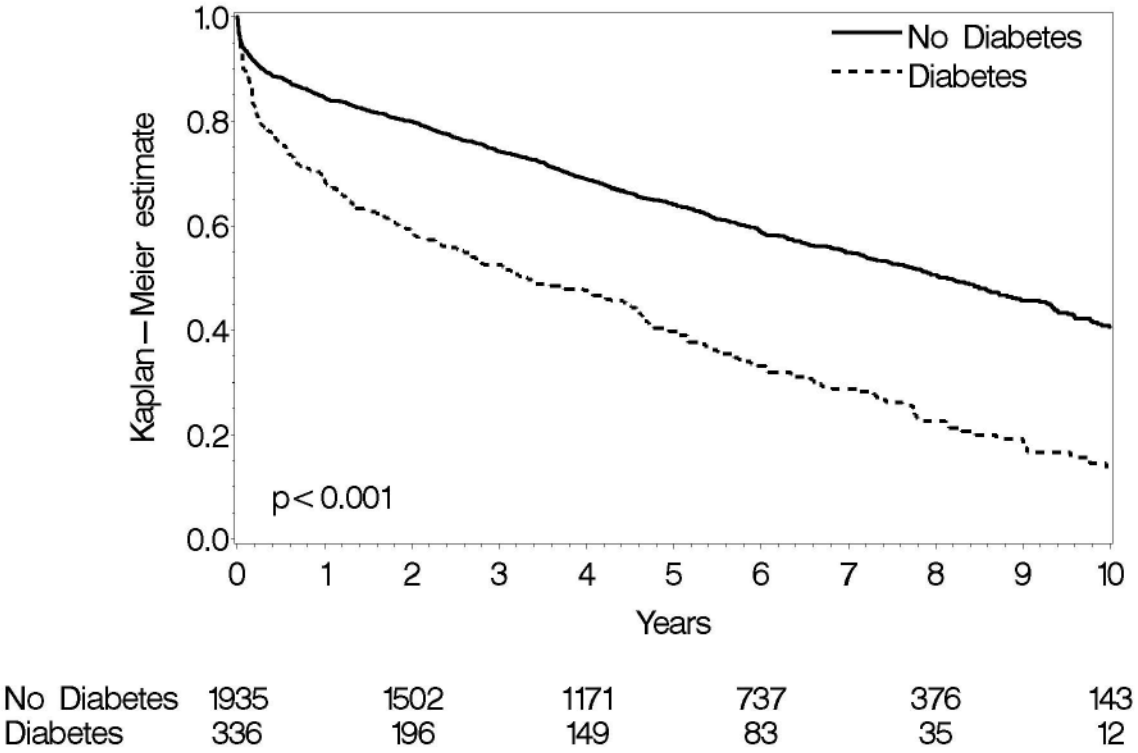


Figure 1.
MACCE Events, DM vs. no DM. The number at risk is reported at 0, 2, 4, 6, 8, and 10 years.

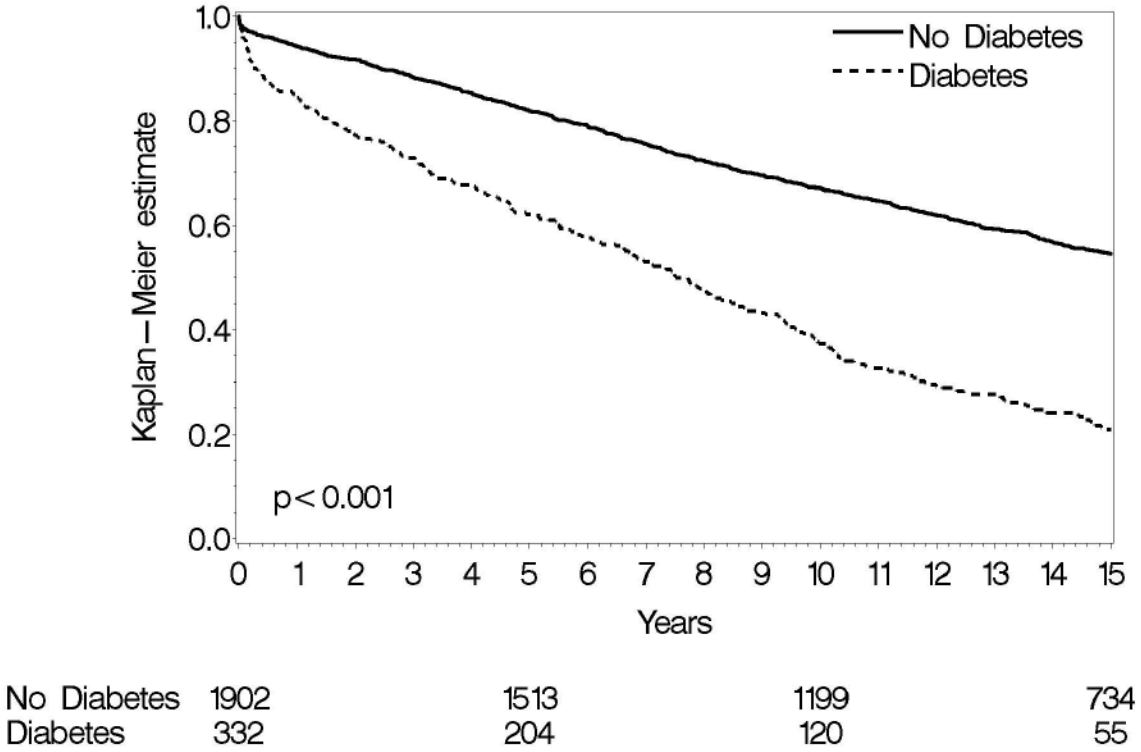
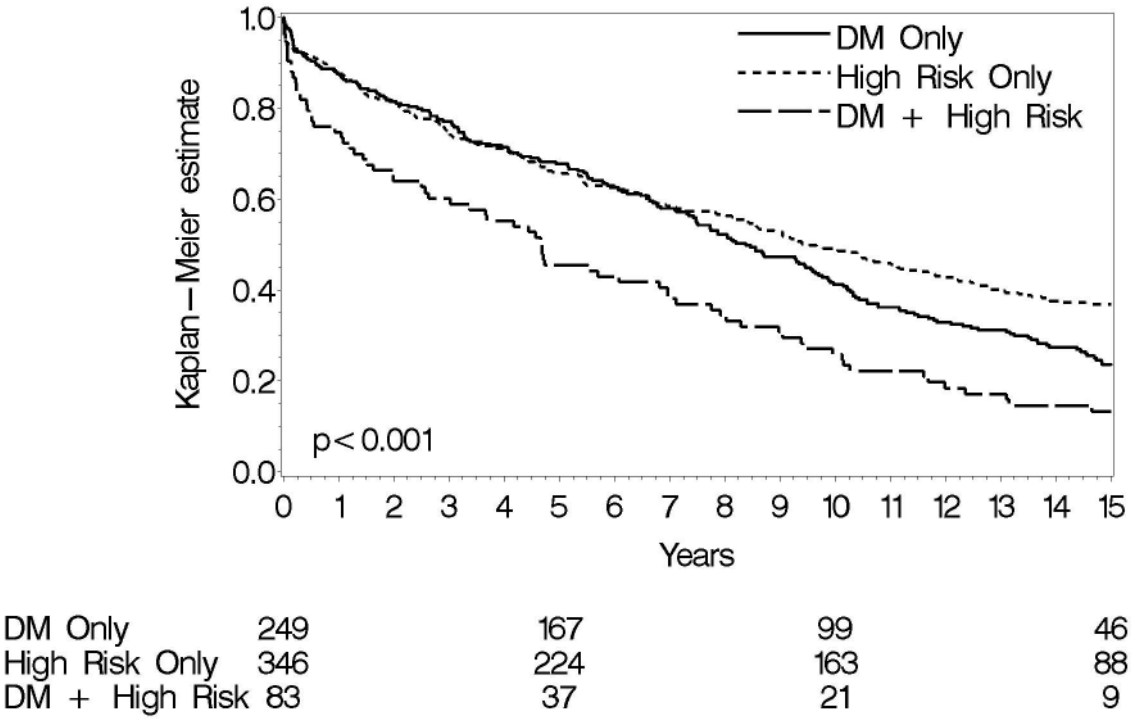


Figure 2.
Mortality, DM vs. no DM. The number at risk is reported at 0, 5, 10, and 15 years.



DM Only	249	167	99	46
High Risk Only	346	224	163	88
DM + High Risk	83	37	21	9

Figure 3.
Mortality, DM vs. AHCPR High-Risk Patients. The number at risk is reported at 0, 5, 10, and 15 years.

Table 1
Baseline Characteristics of Diabetic vs. Non-Diabetic Patients

Characteristics	Total	Diabetes Mellitus		P Value
	2271	Yes 336 (14.8%)	No 1935 (85.2%)	
Mean Age in Years (Range)	63 (21-101)	68 (31-95)	62 (21-101)	<.001
Men	1306 (57.5%)	178 (53.0%)	1128 (58.3%)	0.07
Previous Myocardial Infarction	490 (21.6%)	113 (33.6%)	377 (19.5%)	<.001
Previous Unstable Angina	201 (8.9%)	47 (14.0%)	154 (8.0%)	<.001
Previous Stable Angina	679 (29.9%)	146 (43.5%)	533 (27.5%)	<.001
Incidence Cases *	1352 (59.5%)	145 (43.2%)	1207 (62.4%)	<.001
Current Smoking	490 (21.6%)	41 (12.2%)	449 (23.2%)	<.001
Hypertension **	1039 (45.8%)	228 (67.9%)	811 (41.9%)	<.001
Hypercholesterolemia ***	794 (35.0%)	119 (35.4%)	675 (34.9%)	0.85
Aspirin Use (pre)	395 (17.4%)	74 (22.0%)	321 (16.6%)	0.015
Admitted	2174 (95.7%)	327 (97.3%)	1847 (95.5%)	0.12
Any Electrocardiogram Abnormality	1257 (55.4%)	232 (69.0%)	1025 (53.0%)	<.001
Left Bundle Branch Block	102 (4.5%)	18 (5.4%)	84 (4.3%)	0.41
Family History of Coronary Heart Disease	588 (25.9%)	95 (28.3%)	493 (25.5%)	0.28
Mean (range) Systolic Blood Pressure @ Index Date (mmHg)	153 (60-300)	158 (80-230)	152 (60-300)	<.001
Mean (range) Diastolic Blood Pressure @ Index Date (mmHg)	87 (34-170)	86 (43-150)	88 (34-170)	0.035
Unstable Angina as Discharge Diagnosis	260 (11.4%)	65 (19.4%)	195 (10.1%)	<.001
Non ST Elevation Myocardial Infarction as Discharge Diagnosis	479 (21.1%)	90 (26.8%)	389 (20.1%)	0.006

* Index episode as first presentation with chest pain

** Defined by systolic blood-pressure >140 mmHg or diastolic blood-pressure>90 mmHg

*** Defined by total cholesterol > 220 mg/dL

Table 2

30-day Unadjusted Major Adverse Cardiovascular and Cerebrovascular Events in Diabetic versus Non-Diabetic Patients

Event	Total	Diabetes Mellitus		P-value
	(n=2271)	Yes (n=336)	No (n=1935)	
Total death	57 (2.5%)	14 (4.2%)	43 (2.2%)	0.035
Cardiovascular death	50 (2.2%)	11 (3.3%)	39 (2.0%)	0.147
Myocardial Infarction	47 (2.1%)	6 (1.8%)	41 (2.1%)	0.692
Stroke	14 (0.6%)	6 (1.8%)	8 (0.4%)	0.003
Revascularization	59 (2.6%)	11 (3.3%)	48 (2.5%)	0.399
Percutaneous Coronary Intervention	26 (1.1%)	4 (1.2%)	22 (1.1%)	0.932
Coronary Artery Bypass Graft Surgery	35 (1.5%)	7 (2.1%)	28 (1.4%)	0.382
Heart Failure	93 (4.1%)	33 (9.8%)	60 (3.1%)	<.001
Major Adverse Cardiovascular and Cerebrovascular Events	153 (6.7%)	34 (10.1%)	119 (6.1%)	0.007
Major Adverse Cardiovascular and Cerebrovascular Events or Heart Failure	230 (10.1%)	62 (18.5%)	168 (8.7%)	<.001

Table 3

Long-Term Unadjusted Major Adverse Cardiovascular and Cerebrovascular Events in Diabetic versus Non-Diabetic Patients

	Diabetes Mellitus		No Diabetes Mellitus		
Event	**Total Events**	**K-M (95% CI)**	**Total Events**	**K-M (95% CI)**	**P-value**
Death	151	48.4 (42.4, 53.9)	437	26.4 (24.1, 28.5)	<.001
Cardiac Death	83	29.7 (23.8, 35.1)	215	13.5 (11.8, 15.3)	<.001
Myocardial Infarction	69	27.5 (21.4, 33.1)	225	14.0 (12.2, 15.8)	<.001
Stroke	45	21.0 (14.9, 26.6)	117	8.2 (6.7, 9.7)	<.001
Revascularization	74	27.9 (22.0, 33.3)	320	20.3 (18.2, 22.4)	<.001
Heart Failure	121	45.1 (38.5, 51.1)	285	18.2 (16.2, 20.1)	<.001
Major Adverse Cardiovascular and Cerebrovascular Events	227	71.2 (65.5, 76.0)	779	45.1 (42.6, 47.5)	<.001
Major Adverse Cardiovascular and Cerebrovascular Events or Heart Failure	248	76.9 (71.6, 81.3)	831	47.7 (45.2, 50.1)	<.001

Table 4

Model for Major Adverse Cardiovascular and Cerebrovascular Events in Diabetic Patients at a Median Follow-Up Period of 7.3 Years

Variable	Hazard Ratio	95% Confidence Interval		P-value
Age (years)				<.001
<50	1.000	ref.		
50-59	1.669	1.194	2.333	0.003
60-69	2.327	1.696	3.192	<.001
70-79	3.542	2.585	4.854	<.001
80-89	5.467	3.949	7.570	<.001
90+	9.812	6.788	14.182	<.001
DM effect by age group				0.032
<50	3.192	1.648	6.184	<.001
50-59	1.430	0.846	2.418	0.182
60-69	1.814	1.321	2.492	<.001
70-79	1.406	1.063	1.860	0.017
80-89	1.373	0.986	1.911	0.061
90+	0.796	0.450	1.407	0.432
Female gender	0.691	0.598	0.798	<.001
Diabetes*Female gender	1.371	1.025	1.832	0.033
Prior Myocardial Infarction	1.394	1.215	1.600	<.001
Unstable Angina Pectoris	1.229	1.024	1.474	0.026
Stable Angina Pectoris	1.179	1.036	1.342	0.013
Current Smoker	1.289	1.094	1.519	0.002
Hypertension	1.307	1.150	1.486	<.001
Abnormal Electrocardiogram	1.257	1.097	1.440	<.001
Left Bundle Branch Block	1.449	1.145	1.834	0.002
Systolic Blood Pressure	1.000	0.998	1.002	0.805

Table 5

Model for Mortality at a Median of 16.6 Years in Diabetic Patients Compared to Non-Diabetic Patients

Variable	Hazard Ratio	95% Confidence Interval		P-value
Age (years)				<.001
<50	1.000	ref.		
50-59	1.356	0.749	2.453	0.314
60-69	3.024	1.779	5.139	<.001
70-79	6.372	3.807	10.664	<.001
80-89	16.217	9.701	27.112	<.001
90+	39.446	23.242	66.948	<.001
DM effect by age group				0.003
<50	4.695	1.562	14.117	0.006
50-59	2.318	1.072	5.009	0.033
60-69	2.761	1.923	3.964	<.001
70-79	2.257	1.769	2.879	<.001
80-89	1.654	1.315	2.081	<.001
90+	1.077	0.713	1.627	0.725
Ever Smoked	1.440	1.265	1.639	<.001
Female gender	0.947	0.831	1.079	0.410
Hypertension	1.294	1.144	1.464	<.001
Systolic Blood Pressure	0.997	0.995	0.999	<.001
Hypercholesterolemia	0.999	0.999	1.000	0.268
Family History of Coronary Heart Disease	1.125	0.980	1.292	0.095
Prior Aspirin	0.903	0.781	1.044	0.167
Prior Revascularization	1.340	1.125	1.596	0.001
Prior Myocardial Infarction or History of Coronary Heart Disease	1.572	1.365	1.812	<.001
ST-segment Depression ≥1mm	1.432	1.186	1.728	<.001
Extracardiac Vascular Disease	1.726	1.354	2.200	<.001
Pulmonary Edema Related to Ischemia	1.714	1.402	2.096	<.001