Treatment Disparities in the Care of Patients With and Without Diabetes Presenting With Non–ST-Segment Elevation Acute Coronary Syndromes

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OBJECTIVE — The objective of this study was to characterize treatment patterns among patients with diabetes presenting with non–ST-segment elevation (NSTE) acute coronary syndromes (ACSs).

RESEARCH DESIGN AND METHODS — We compared adherence to treatment recommendations from the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for NSTE ACS among 46,410 patients from 413 U.S. hospitals that were included in the Can Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. Patients were stratified as nondiabetic, non–insulin-dependent diabetic (type 2 diabetic), and insulin-treated diabetic.

RESULTS — Insulin-treated diabetic patients were less likely than nondiabetic patients to receive aspirin (adjusted odds ratio 0.83 [95% CI 0.74–0.93]), β-blockers (0.89 [0.83–0.96]), heparin (0.90 [0.83–0.98]), and glycoprotein IIb/IIIa inhibitors (0.86 [0.79–0.93]). Type 2 diabetic patients were treated similarly to nondiabetic patients. After adjustment for differences in clinical characteristics, insulin-treated diabetic patients were significantly less likely than nondiabetic patients to receive cardiac catheterization within 48 h of presentation (0.80 [0.74–0.86]) or percutaneous coronary intervention (0.87 [0.82–0.94]). Compared with nondiabetic patients, insulin-treated diabetic and type 2 diabetic patients were more likely to undergo coronary artery bypass grafting (1.34 [1.21–1.49] and 1.35 [1.26–1.44]). In-hospital mortality rates were higher in insulin-treated diabetic (6.8%) and type 2 diabetic (5.4%) than in nondiabetic (4.4%) patients.

CONCLUSIONS — Diabetic patients have a higher risk of mortality than nondiabetic patients, yet physicians adhere to the ACC/AHA NSTE ACS guidelines less often when treating diabetic patients, particularly insulin-treated diabetic patients. Increased use of guideline-recommended therapies and early invasive management strategies in diabetic patients may improve their outcomes.

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Compared with nondiabetic patients, patients with diabetes have an increased incidence of acute coronary syndromes (ACSs) and worse cardiovascular outcomes, including an increased cardiovascular mortality rate (1–4). Recent prospective clinical trials supported these observations (5–8). However, these analyses are limited by several factors. Most data have been derived only from assessments of patients with ST-segment elevation myocardial infarction who are eligible for thrombolysis, representing only a minority of ACS patients. Other studies of broader cohorts are limited by their relatively small sample sizes, the small proportions of diabetic patients enrolled, or randomization processes with differing protocol-specified pharmacologic interventions (9).

New findings underscore the importance of intensive treatment of diabetic patients. Several trials have consistently shown larger relative risk reductions for pharmacotherapies in the treatment of ACSs in diabetic patients versus nondiabetic patients. Because the absolute risk is larger in diabetic patients than in nondiabetic patients, the potential absolute benefit will also be larger in diabetic patients (10,11). This fact underscores the importance of using known evidence-based treatment for all ACS patients, especially diabetic patients. The most recent evidence-based guidelines for the treatment of non–ST-segment elevation (NSTE) ACS patients address and emphasize the need for early risk stratification of high-risk patients, early interventional

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Abbreviations: ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; AOR, adjusted odds ratio; CRUSADE, Can Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; NSTE, non–ST-segment elevation; PCI, percutaneous coronary intervention.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline demographic characteristics*

Characteristic	Nondiabetic	Type 2 diabetic	Insulin-treated diabetic	*P* value
Age (years)	67 ± 15	69 ± 13	67 ± 13	<0.0001
Age <45 years	8.7	3.9	4.7	<0.0001
Male sex	61	59	51	<0.0001
African American	10	12	19	<0.0001
Current/recent smoker	31	22	18	<0.0001
Hypertension	63	80	81	<0.0001
Prior myocardial infarction	27	36	43	<0.0001
Prior PCI	19	25	27	<0.0001
Prior coronary artery bypass grafting	17	25	31	<0.0001
Renal insufficiency*	9	18	32	<0.0001
Hypercholesterolemia	43	53	52	<0.0001
Presenting features				
Median duration of symptoms (h)	2.75	2.92	3.00	
Mean duration of symptoms (h)	6.75	7.15	7.54	NS
Mean heart rate (bpm)	84	89	90	<0.0001
Mean systolic blood pressure (mmHg)	144	148	146	<0.0001
Heart failure on presentation	18	28	36	<0.0001
Positive cardiac markers	88	87	88	NS

Data are means ± SD or % unless otherwise indicated. Smoker indicates current or recent (within previous 6 weeks) tobacco smoking habit, hypertension indicates systolic blood pressure >160 mmHg or diastolic blood pressure >95 mmHg or treatment with antihypertensive agents, and hypercholesterolemia indicates total cholesterol >200 mg/dl or treatment with lipid-lowering agents. *Serum creatinine >2.0 mg/dl, estimated creatinine clearance <30 ml/min, or need for dialysis.

management, and aggressive antiplatelet and antithrombotic therapy.

We sought to evaluate adherence to the American College of Cardiology (ACC)/American Heart Association (AHA) NSTE ACS treatment guidelines and differences in clinical outcomes among patients with and without diabetes included in the Can Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) national quality improvement initiative.

RESEARCH DESIGN AND METHODS

— We evaluated 46,410 patients from 413 U.S. hospitals who presented with NSTE ACS (positive cardiac markers or ischemic ST-segment changes) and were included in the CRUSADE national quality improvement initiative. CRUSADE is a prospective registry that was previously described in the literature; it includes patients who have chest pain or angina equivalent at rest for at least 10 min in duration within 24 h of presentation and either ischemic electrocardiographic changes (ST-segment depression >0.5 mm or transient ST-segment elevation of 0.5–1.0 mm for <10 min in duration) or elevated levels of markers of myocardial necrosis (creatinine kinase–myocardial band or troponin) (12). CRUSADE measures both the emergency department use of acute pharmacologic modalities (such as aspirin, heparin, β-blockers, and platelet inhibitors) and the in-hospital use of interventional therapies as recommended in the ACC/AHA 2002 guidelines as well as recommended discharge therapies. Patients are followed throughout their hospitalization to determine outcomes. Adherence to ACC/AHA guidelines was determined, taking into account both indications and contraindications for each individual patient. For example, utilization of β-blockers in the CRUSADE patient population was assessed only for those patients with indications for β-blockade.

After institutional review board approval was obtained at each site, the CRUSADE registry analyzed patient records to determine compliance with 2002 ACC/AHA guidelines for patients with NSTE ACS. Patients were stratified as nondiabetic, non–insulin-dependent diabetic (diabetes controlled by diet or oral medication, type 2 diabetes), or insulin-treated diabetic (diabetes being treated with insulin). Treatment recommendations from the ACC/AHA guidelines were reviewed, and utilization rates were compared among these groups. In addition, patients were followed throughout hospitalization for important clinical outcome measures including death, nonfatal myocardial infarction, and heart failure.

Statistical analysis

Data were reported as medians (25th and 75th percentiles) for continuous variables and frequencies for categorical variables. Kruskal-Wallis and χ^2 tests were used to evaluate differences in continuous and categorical variables, respectively. Differences in utilization of acute therapies and clinical outcomes are presented as adjusted odds ratios (AORs) with 95% CIs.

Odds ratios were adjusted for age; sex; race; past medical history (prior myocardial infarction, percutaneous coronary intervention [PCI], coronary artery bypass grafting, congestive heart failure, stroke, or renal insufficiency [defined as creatinine >2 mg/dl, creatinine clearance <30 ml/min, or dialysis dependence]); electrocardiogram findings; cardiac marker results; presenting vital signs; insurance status; and hospital size, type, academic status, location, and percutaneous and surgical revascularization capabilities. To evaluate the effect of controlling for renal insufficiency, we also compared treatments and outcomes after excluding patients with renal insufficiency.

The Duke Clinical Research Institute (Durham, NC) coordinated data input and analysis. $P < 0.05$ was established as the level of statistical significance for all tests. All analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC).

RESULTS

— Of the 46,410 patients presenting with NSTE ACS, 31,049 were nondiabetic, 9,773 were type 2 diabetic, and 5,588 were insulin-treated diabetic. Baseline characteristics are listed in Table 1. Patients with type 2 diabetes and insulin-treated diabetes were older, were less commonly male, and more commonly had renal insufficiency and signs of congestive heart failure on presentation compared with nondiabetic patients.

Differences in usage of acute medication therapy and interventions are summarized in Tables 2 and 3. Insulin-treated diabetic patients were less likely than nondiabetic patients to receive aspirin (AOR 0.83 [95% CI 0.74–0.93]), β-blockers (0.89 [0.83–0.96]), heparin (0.90 [0.83–0.98]), and glycoprotein IIb/IIIa inhibitors (0.86 [0.79–0.93]). Type 2 diabetic patients received these medical therapies at a rate approximately equal to

Table 2—*Acute (<24 h) medications

Pharmacologic treatment	Nondiabetic	Type 2 diabetic	Insulin-dependent diabetic	AOR (95% CI) Type 2 diabetic†	AOR (95% CI) Insulin-treated diabetic‡
n	31,049	9,773	5,588		
Aspirin (%)	91.7	90.6	88.4	0.94 (0.87–1.02)	0.83 (0.74–0.93)
β-Blockers (%)	77.8	78.7	75.3	1.01 (0.95–1.08)	0.89 (0.83–0.96)
Heparin (%)§	83.2	82.3	77.9	1.02 (0.96–1.08)	0.90 (0.83–0.98)
Glycoprotein IIb/IIIa inhibitor (%)	37.4	32.2	25.1	0.99 (0.94–1.06)	0.86 (0.79–0.93)
Clopidogrel (%)	40.8	37.4	34.7	0.94 (0.89–0.99)	0.97 (0.91–1.03)

*For patients without listed contraindications to the given medication. †Nondiabetic vs. type 2 diabetic. ‡Nondiabetic vs. insulin-treated diabetic. §Includes both unfractionated and low–molecular weight heparin.

that of nondiabetic patients. Type 2 diabetic patients were less likely than nondiabetic patients to receive clopidogrel (0.94 [0.89–0.99]). Although not statistically significant, usage of clopidogrel was lower in insulin-treated diabetic patients than in nondiabetic patients (0.97 [0.91–1.02]).

In addition, insulin-treated diabetic patients were less likely to receive cardiac catheterization, cardiac catheterization within 48 h of presentation, PCI, or PCI within 48 h. A similar trend was noted in the type 2 diabetes group, but this did not reach statistical significance. Insulin-treated diabetic and type 2 diabetic patients were more likely to undergo coronary artery bypass grafting (AOR 1.34 [95% CI 1.21–1.49] and 1.35 [1.26–1.44]) compared with nondiabetic patients.

Differences in clinical outcomes are summarized in Table 4. In-hospital mortality rates were higher in insulin-treated diabetic (6.8%) and type 2 diabetic (5.4%) patients than in nondiabetic (4.4%) patients. Rates of congestive heart failure (13.7 vs. 12.4 vs. 8.0%) and the need for erythrocyte transfusion during hospitalization (30.8 vs. 17.4 vs. 12.9%) were higher as well.

ACE inhibitors were more likely to be prescribed at discharge for type 2 diabetic and insulin-treated diabetic patients than for nondiabetic patients (AOR 1.33 [95% CI 1.26–1.40] and 1.37 [1.27–1.47]) (Table 5). β-Blocker, aspirin, lipid-lowering agent, and clopidogrel therapies were equally likely to be used at discharge for all three groups (Table 5). Whereas insulin-treated diabetic and type 2 diabetic patients were more likely to receive dietary counseling, they were less likely to receive smoking cessation counseling, although the difference was statistically significant only for insulin-treated diabetic patients.

After exclusion of patients with renal insufficiency (serum creatinine >2.0 mg/dl, estimated creatinine clearance <30 ml/min, or need for dialysis), similar treatment disparities for certain medications and procedures were demonstrated. Acute (within 24 h) aspirin was used in 92.1% of nondiabetic patients, 91.2% of type 2 diabetic patients, and 89.1% of insulin-treated diabetic patients; heparin in 83.9, 83.1, and 79.8%; glycoprotein IIb/IIIa inhibitors in 38.8, 34.2, and 26.9%; and early catheterization (within 48 h) in 52.0, 46.6, and 37.5%. Discharge aspirin and clopidogrel were used in 90.6 and 54.6% of nondiabetic patients, 89.7 and 51.4% of type 2 diabetic patients, and 87.8 and 48.0% of insulin-treated diabetic patients. The rates of death and of the composite end point of death or reinfarction were lowest in nondiabetic patients (3.7 and 6.3%) compared with type 2 diabetic patients (4.5 and 7.1%) and insulin-treated diabetic patients (5.8 and 8.7%) after patients with renal insufficiency were excluded.

CONCLUSIONS

Pathophysiologic alterations in diabetes

Both insulin-treated diabetes and type 2 diabetes are independent risk factors for coronary artery disease, stroke, and peripheral arterial disease (13,14). Diabetes induces alterations in the coagulation cascade with a shift toward a more prothrombotic state as well as an increase in platelet aggregation and adhesion (15,16). Autopsies have shown that diabetic patients have a more diffuse distribution of atherosclerotic lesions (17,18). Diabetic patients with established coronary artery disease undergoing cardiac catheterization for acute myocardial infarction, angioplasty, or coronary artery

Table 3—*Invasive cardiac procedures*

Acute intervention	Nondiabetic	Type 2 diabetic	Insulin-dependent diabetic	AOR (95% CI) Type 2 diabetic†	AOR (95% CI) Insulin-treated diabetic‡
n	31,049	9,773	5,588		
Catheterization (%)	68.4	64.6	56.3	1.05 (0.99–1.11)	0.94 (0.86–1.02)
Catheterization <48 h (%)	49.3	42.4	31.8	0.98 (0.93–1.04)	0.80 (0.74–0.86)
PCI (%)	39.1	33.4	26.4	0.97 (0.92–1.02)	0.87 (0.82–0.94)
PCI <48 h (%)	29.0	22.2	15.5	0.93 (0.87–0.98)	0.79 (0.73–0.87)
Coronary artery bypass grafting (%)	11.5	13.1	10.0	1.35 (1.26–1.44)	1.34 (1.21–1.49)

*Nondiabetic vs. type 2 diabetic. †Nondiabetic vs. insulin-treated diabetic.

Table 4—*In-hospital clinical outcomes*

Clinical outcome	Nondiabetic	Type 2 diabetic	Insulin-dependent diabetic	AOR (95% CI) Type 2 diabetic*	AOR (95% CI) Insulin-treated diabetic†
n	31,049	9,773	5,588		
Death (%)	4.4	5.4	6.8	1.14 (1.02–1.29)	1.29 (1.12–1.49)
Reinfarction (%)	3.2	3.5	3.8	1.07 (0.96–1.19)	1.07 (0.93–1.24)
Congestive heart failure (%)	8.0	12.4	13.7	1.25 (1.16–1.34)	1.19 (1.09–1.31)
Shock (%)	2.5	3.2	3.5	1.22 (1.05–1.41)	1.18 (0.97–1.44)
Red blood cell transfusion (%)	12.9	17.4	20.8	1.31 (1.23–1.40)	1.51 (1.40–1.63)

*Nondiabetic vs. type 2 diabetic. †Nondiabetic vs. insulin-dependent diabetic.

bypass grafting have significantly more severe proximal and distal coronary artery disease (5,19–21). In addition, postmortem and angioscopic evidence indicates an increase in ulcerated plaque morphology in diabetic patients (22,23). McGuire et al. (24) demonstrated a significantly increased 30-day rate of reinfarction in diabetic patients without ST-segment elevation on initial presentation compared with that in nondiabetic patients (9.0 vs. 5.3%, $P < 0.0001$). Effective use of antiplatelet and antithrombotic agents as recommended in the guidelines could be expected to address the underlying pathophysiologic process in diabetic patients.

CRUSADE results

Our study demonstrates that both type 2 diabetic and insulin-treated diabetic patients are at increased risk of death compared with nondiabetic patients. Despite this increased risk, insulin-treated diabetic patients are less likely to be treated with antiplatelet and antithrombotic agents (aspirin, heparin, glycoprotein IIb/IIIa inhibitors, and β-blockers) and less likely to undergo cardiac catheterization and/or PCI, especially within 48 h. Even when patients with renal insufficiency were excluded, treatment disparities remained: specifically, decreased utilization of aspirin, heparin, and glycoprotein IIb/IIIa inhibitors and early catheterization in insulin-treated diabetic patients compared with type 2 diabetic and nondiabetic patients. Similar trends were seen with discharge therapies such as aspirin and clopidogrel.

Our data are consistent with data from other clinical trials that evaluated acute myocardial infarction patients (but excluded high-risk unstable angina patients) before the use of newer agents such as low–molecular weight heparin and glycoprotein IIb/IIIa inhibitors (25). Berger et al. 25, who evaluated only patients >65 years of age, further demonstrated that diabetic patients, particularly those taking insulin, were less likely to receive aspirin or β-blockers and undergo coronary revascularization. Both type 2 diabetic and insulin-treated diabetic patients had higher 30-day and 1-year mortality than did nondiabetic patients, even after adjustment for demographic, clinical, hospital, and therapeutic differences. After adjustment for demographics, clinical and hospital characteristics, and treatment strategies, insulin-treated diabetic patients had the highest risk of mortality, followed by diabetic patients receiving oral hyperglycemic agents, followed by patients with diet-controlled diabetes. Mortality rates were significantly higher in these diabetic patients than in their nondiabetic counterparts. This led to a call for "preventative and therapeutic strategies targeted specifically at improving outcomes for diabetic patients." Our data suggest that in a very broad NSTE ACS high-risk population, this call has gone unheeded.

Future directions

The underutilization of various medical therapies (i.e., aspirin and β-blockers) and cardiac procedures (such as cardiac catheterization and coronary angioplasty) among diabetic patients raises clinical practice concerns because the efficacy of these therapies among diabetic patients has been validated in prior studies

Table 5—*Discharge therapies**

Discharge therapy	Nondiabetic	Type 2 diabetic	Insulin-dependent diabetic	AOR (95% CI) Type 2 diabetic†	AOR (95% CI) Insulin-treated diabetic‡
n	31,049	9,773	5,588		
ACE inhibitor (%)§	52.6	63.2	64.1	1.33 (1.26–1.40)	1.37 (1.27–1.47)
β-Blocker (%)	82.4	84.2	81.6	1.06 (0.99–1.14)	0.94 (0.87–1.01)
Aspirin (%)	90.2	88.9	86.9	0.95 (0.88–1.04)	0.90 (0.81–1.01)
Statin (%)‖	61.0	63.0	60.2	1.04 (0.98–1.10)	0.98 (0.90–1.06)
Clopidogrel (%)	53.4	50.3	46.6	0.98 (0.93–1.03)	0.95 (0.89–1.02)
Dietary counseling (%)	70.0	72.8	71.1	1.19 (1.13–1.24)	1.16 (1.09–1.24)
Cardiac rehabilitation referral (%)	41.5	39.6	34.7	1.05 (1.00–1.10)	0.99 (0.92–1.07)
Smoking cessation counseling (%)	65.7	59.3	52.2	0.93 (0.85–1.02)	0.76 (0.68–0.86)

*In patients without listed contraindications to the given medications. †Nondiabetic vs. type 2 diabetic. ‡Nondiabetic vs. insulin-dependent diabetic. §Patients with congestive heart failure, ejection fraction <40%, diabetes, and hypertension. ‖Patients with documented hyperlipidemia or LDL cholesterol >100 mg/dl.

(26,27). Previous studies have suggested that the lower utilization of these more recent antiplatelet and antithrombotic therapies may be explained by a higher prevalence of comorbid disease and/or contraindications. However, we controlled for these variables (e.g., renal insufficiency) in our study, and significant differences in utilization of both medical and invasive acute treatments still persisted.

Our study also represents a real-world sample of how diabetic patients are managed for NSTE ACS. Previous studies evaluating treatment of diabetic patients either focused on the ST-segment elevation myocardial infarction population alone or specifically excluded patients <65 years of age (25). The relatively high prevalence of diabetes in our cohort (30%, consistent with the prevalence in an age-matched general population) compared with those observed in other clinical trials demonstrates that diabetic patients are underrepresented in clinical trial enrollment. This is a major strength of our study design. Thus, quality initiatives such as the CRUSADE registry highlight opportunities for improving care in the diabetic population.

Limitations

Our analysis has several limitations. First, we could not verify whether hospitals included consecutive patients with NSTE ACS, so the results may be subject to a sampling bias. Second, because this is an observational study, one cannot draw firm conclusions regarding cause and effect between less acute treatment and higher mortality. Third, we did not assess the relationship between the severity of the patient's diabetes and outcomes. Insulin-treated diabetic patients presumably had a more severe form of diabetes than did type 2 diabetic patients, but factors such as the duration of diabetes could not be assessed from the database, and HbA_{1c} was not measured. Lastly, the insulin-treated diabetic group represents a group of patients composed of insulin-dependent type 1 patients and type 2 patients currently being treated with insulin.

Summary

Diabetic patients have a higher risk of mortality than do nondiabetic patients, yet physicians adhere to the ACC/AHA NSTE ACS guidelines less often when treating diabetic patients, particularly insulin-treated diabetic patients. Increased use of guidelines-recommended therapies and early invasive management strategies in diabetic patients may improve the outcomes of these high-risk patients and should be evaluated in a clinical trial format.

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