Discontinuation of Antihyperglycemic Therapy and Clinical Outcomes After Acute Myocardial Infarction in Older Patients With Diabetes

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Background—Patients with diabetes are frequently admitted for acute myocardial infarction (AMI) on antihyperglycemic agents but may be discharged without glucose-lowering therapy. We examined the frequency of this practice and evaluated the associated outcomes of readmission and mortality.

Methods and Results—We conducted a retrospective study of 24,953 Medicare beneficiaries with diabetes discharged after hospitalization for AMI. We examined the frequency of discontinuation of antihyperglycemic agents on discharge among those patients admitted on a diabetic regimen. The independent association between discharge on versus off antihyperglycemic therapy and outcomes at 1 year was assessed in multivariable Cox proportional hazards models, adjusting for patient, physician, and hospital variables. The primary outcome was time to death within 1 year of discharge; secondary outcomes were time to first rehospitalization within 1 year for AMI, heart failure, and all causes. There were 8,751 patients admitted on at least 1 antihyperglycemic agent who met our inclusion/exclusion criteria. Of these, 7,581 (86.6%) were discharged on antihyperglycemic therapy and 1,170 (13.4%) were discharged off antihyperglycemic therapy. After multivariable analysis, as compared with those whose diabetes therapy was continued at discharge, patients who were not prescribed a glucose-lowering agent had higher 1-year mortality rate (hazard ratio, 1.29; 95% confidence interval, 1.15 to 1.45). Readmission rates did not differ significantly between the 2 groups (hazard ratio, 0.95; 95% confidence interval, 0.87 to 1.03).

Conclusions—In older patients with diabetes after AMI, discontinuation of antihyperglycemic therapy is common and associated with higher mortality rates. The reasons behind this practice as well as the specific effects of hyperglycemia after AMI merit further study. (Circ Cardiovasc Qual Outcomes. 2010;3:236-242.)

Key Words: acute myocardial infarction • diabetes mellitus • antihyperglycemic medication • hospital discharge

Many investigations have demonstrated that hyperglycemia during acute myocardial infarction (AMI) predicts adverse outcomes and mortality in patients with diabetes.1,2 Whether hyperglycemia mediates those events or is merely a marker for underlying metabolic derangement or for the degree of illness (eg, extent of infarction) remains unclear. Several studies have focused on intensive blood glucose (BG) control during admission for AMI with variable results.3–7 Fewer data exist on the quality of glucose management shortly after hospital discharge after a cardiovascular event and its association with patient outcomes. Furthermore, recent trials evaluating long-term intensive glycemic control in patients with diabetes have raised doubts regarding the efficacy of such strategies for prevention of cardiovascular events, particularly in older patients with established macrovascular disease.8–10

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Antihyperglycemic agents are often held during hospitalization for a variety of reasons and sometimes may not be resumed at hospital discharge. In many cases, this may be appropriate given the uncertainties regarding a patient’s

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nutritional intake, the trajectory of BG levels, and new contraindications to therapy. However, the implications of this practice on clinical outcomes are not known. Using data from the National Heart Care Project, a Centers for Medicare and Medicaid Services initiative designed to assess and improve the quality of care after AMI, we studied Medicare beneficiaries with diabetes mellitus hospitalized for AMI and examined the association between discontinuation of antihyperglycemic therapy and outcomes of mortality and readmission at 1 year.

WHAT IS KNOWN

- Hyperglycemia has been associated with adverse outcomes during acute myocardial infarction.
- Multiple trials of intensive glucose control in patients with prior history of myocardial infarction have yielded conflicting results, but most did not examine the quality of blood glucose control shortly after discharge.

WHAT THE STUDY ADDS

- We found that 1 of 8 patients with type 2 diabetes is admitted on, but discharged off antihyperglycemic therapy.
- This practice is associated with increased mortality up to 1 year after discharge.
- Future studies should examine the reasons behind the discontinuation of antihyperglycemic therapy and the potential direct effects of glucose control on outcomes after acute myocardial infarction.

Methods

Data Sources

The National Heart Care Project

The National Heart Care Project is a Centers for Medicare and Medicaid Services initiative designed to assess and improve the quality of care for Medicare beneficiaries with AMI. The data for the project consist of 2 longitudinal national cohorts of fee-for-service Medicare beneficiaries hospitalized with a principal discharge diagnosis of AMI. The first sample included hospitalizations with discharge dates between April 1998 and March 1999, inclusive, and the second between July 2000 and June 2001, inclusive. All admissions in each of the 50 states, Washington, DC, and Puerto Rico identified within these time frames were sorted by age, sex, race, and hospital; up to 800 records from each state were included. Detailed demographic and clinical data were abstracted from these records by trained medical record reviewers. Data quality was enhanced through the use of medical record abstraction software and random reabstraction.

Additional Data Sources

The sample cohort was linked with the American Medical Association Physician Masterfile and to the American Hospital Association Annual Surveys to ascertain the characteristics of the attending physicians and hospitals. Dates of death were assessed through linkage with the Medicare Enrollment Database. Linkage with Part A Medicare data provided the dates and diagnoses for rehospitalizations occurring within 1 year of the index hospitalization.

Patients

The cohort consisted of 35,713 records in 1998 to 1999 and 35,407 in 2000 to 2001, for a total of 71,120 records. A clinical diagnosis of AMI was confirmed using standard clinical, ECG, and laboratory criteria.

Candidates for this study were those patients with a diagnosis of diabetes (n = 17,570) established by the prescription of an antihyperglycemic medication at admission. We excluded discharges in which a diagnosis of AMI could not be confirmed (n = 1,682), patients died during the hospitalization (n = 2,099), patients had unknown dates of death (n = 121) or unknown readmission data (n = 783), patients were transferred to another hospital (n = 3,221) or left against medical advice (n = 60), patients had multiple discharges (first discharge was included, subsequent hospitalizations were analyzed in the readmission outcomes) (n = 793), and patients were younger than 65 years (n = 2,091), as these discharges may not be representative of the Medicare population. After the exclusion criteria were applied, a total of 8,751 records were assessed.

Measurements

Variables

The main independent variable was the prescription of antihyperglycemic agents (oral agents and/or insulin) at hospital discharge.

Outcomes

The primary outcome variable was time from hospital discharge to death from any cause, up to 1 year after discharge. Secondary outcomes included 30-day and 6-month mortality, time to first readmission for myocardial infarction, for heart failure, and for any cause, up to 1 year after discharge. Patients who died were censored in the readmission analyses.

Statistical Analysis

Primary Analysis

Patients were categorized into 2 mutually exclusive groups by their antihyperglycemic drug status: those prescribed any antihyperglycemic regimen on discharge versus those who were discharged without glucose-lowering medications. Differences in the characteristics of patient, physician, and hospital were compared using a chi-square test for categorical variables and a t test for continuous variables. Independent effect of the antihyperglycemic prescription at discharge on outcomes was evaluated using the multivariable proportional hazard Cox models adjusting for the following factors: demographics (age, sex, and race); cardiac history (history of heart failure, myocardial infarction, hypertension, cerebral vascular accident, and revascularization); noncardiovascular history (diabetes complications, admission source, mobility, chronic pulmonary disease, urinary incontinence, and dementia); clinical characteristics at hospital admission (systolic blood pressure, respiratory rate, heart failure, sodium, BUN, creatinine, white blood count, and hematocrit); admission antihyperglycemic regimen (sulfonylureas, biguanides, thiazolidinediones, glinides, α-glucosidase inhibitors, and insulin); admission and discharge prescriptions for cardiac medications (aspirin, ACE inhibitors, β-adrenergic receptor blockers, calcium channel blockers, statins, and fibrates); hospital course (atrial fibrillation, heart failure/pulmonary edema on admission chest radiograph, left ventricular (LV) systolic function, cardiac catheterization, percutaneous coronary intervention (PCI), coronary artery bypass grafting [CABG], diabetic complications); discharge disposition (home, extended-care facility, skilled nursing facility, intermediate-care facility, and other); the sample period in which the index hospitalization occurred; attending physician (specialty and board certification) and the treating hospital (bed size, geographic location, ownership, level of cardiac facilities, and teaching status). Importantly, adjustment was also made for admission BG based on 4 categories: <136 mg/dL, 136 to 185 mg/dL, 186 to 250 mg/dL, and >250 mg/dL; and

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This practice is associated with increased mortality up to 1 year after discharge.

Future studies should examine the reasons behind the discontinuation of antihyperglycemic therapy and the potential direct effects of glucose control on outcomes after acute myocardial infarction.

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diabetic complications, as identified by ICD-9 codes within 1 year before admission or during the current admission (including peripheral vascular disease and diabetic nephropathy, retinopathy, and neuropathy.) These factors were chosen based on both clinical and statistical (P<0.05) significance. The models also accounted for clustering of patients by hospitals.

Secondary Analyses
Because some antihyperglycemic agents were not recommended at the time the study was conducted in patients with advanced heart failure, analyses were stratified by the presence or absence of heart failure/pulmonary edema on admission chest radiograph and by the presence of LV systolic dysfunction. Similarly, analyses were stratified by revascularization status because certain agents may be contraindicated soon after cardiac catheterization. Because of concerns that failure to restart diabetic therapy might occur more commonly in those requiring intermediate/long-term care, analyses were also stratified by discharge disposition.

Statistical analyses were performed with SAS 9.1 (SAS Inc, Cary, NC) and Stata 10.0 (Stata Corporation, College Station, Tex). The use of the NHC database was approved by the Yale University Human Investigation Committee.

Results
Patients
Among the 8751 patients admitted on at least 1 antihyperglycemic agent, 7581 patients (86.6%) were discharged on diabetic medications whereas 1170 (13.4%) were discharged off diabetic medications. The mean age of the cohort was 76.5±7.1 years, the majority being Caucasian (80.6%) and female (52.8%). Compared with patients discharged on a pharmacological antihyperglycemic regimen, those discharged off medications were older and significantly more likely to be nonwhite (see Table 1). They were also less likely to have a prior history of MI, hypertension, or CABG but more likely to carry the diagnosis of chronic obstructive pulmonary disease, dementia, urinary incontinence, or dialysis dependence. With respect to admission characteristics, there were no differences in presentation with ST-elevation MI, anterior MI, or heart failure/pulmonary edema on chest radiograph between the 2 groups. However, there were proportionately more patients with impaired LV systolic function in the group discharged off antihyperglycemic therapy. Mean glucose levels were lower in the group discharged off glucose lowering medications (219.5±104.7 mg/dL versus 242.3±120.1 mg/dL, P<0.0001), but rates of hypoglycemia on admission (defined as BG <70 mg/dL) did not differ between the 2 groups (2.0% in the off versus 1.8% in the on diabetic medication group, respectively, P=0.63). In addition, those patients discharged without antihyperglycemic therapy were less likely to have been admitted on aspirin, β-blocker, ACE inhibitor, or statin.

During the hospitalization, there were no differences in primary reperfusion between the 2 groups, although fewer patients in the off-therapy group underwent cardiac catheterization. Significantly fewer patients in this group were discharged on aspirin, β-blocker, ACE inhibitor, or statin. The majority of patients in both groups were discharged to home (74.5%), but proportionately fewer off-therapy patients had this discharge disposition (63.5%) compared with those discharged on a pharmacological antihyperglycemic regimen (76.2%).

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Discharged Off Medications</th>
<th>Discharged On Medications</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>77.1±7.5</td>
<td>76.5±7.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Female</td>
<td>54.0</td>
<td>52.7</td>
<td>0.39</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>23.6</td>
<td>18.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>42.8</td>
<td>40.9</td>
<td>0.22</td>
</tr>
<tr>
<td>MI</td>
<td>40.4</td>
<td>45.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76.7</td>
<td>80.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>23.8</td>
<td>24.0</td>
<td>0.88</td>
</tr>
<tr>
<td>CABG</td>
<td>19.7</td>
<td>23.5</td>
<td>0.003</td>
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<tr>
<td>PCI</td>
<td>15.3</td>
<td>16.5</td>
<td>0.32</td>
</tr>
<tr>
<td>Noncardiac history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive</td>
<td>25.6</td>
<td>21.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia/Alzheimer disease</td>
<td>10.6</td>
<td>8.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Urinary continence</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unknown</td>
<td>29.0</td>
<td>31.3</td>
<td></td>
</tr>
<tr>
<td>Continent</td>
<td>52.5</td>
<td>55.0</td>
<td></td>
</tr>
<tr>
<td>Incontinent or on dialysis</td>
<td>18.5</td>
<td>13.7</td>
<td></td>
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<tr>
<td>Diabetic complications</td>
<td>13.0</td>
<td>13.4</td>
<td>0.72</td>
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<tr>
<td>Admission source</td>
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<td></td>
<td></td>
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<tr>
<td>Home</td>
<td>64.4</td>
<td>65.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Long-term facility (skilled nursing facility, extended care facility, intermediate-care facility)</td>
<td>9.9</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Outpatient setting</td>
<td>6.9</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>18.8</td>
<td>19.3</td>
<td></td>
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<tr>
<td>Admission antihyperglycemic agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>55.9</td>
<td>55.8</td>
<td>0.96</td>
</tr>
<tr>
<td>Metformin</td>
<td>16.6</td>
<td>22.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>8.7</td>
<td>12.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Insulin</td>
<td>39.0</td>
<td>43.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Presenting features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-elevation on ECG</td>
<td>23.9</td>
<td>23.7</td>
<td>0.89</td>
</tr>
<tr>
<td>Congestive heart failure/ pulmonary edema</td>
<td>30.3</td>
<td>30.6</td>
<td>0.82</td>
</tr>
<tr>
<td>Anterior AMI</td>
<td>31.2</td>
<td>30.5</td>
<td>0.62</td>
</tr>
<tr>
<td>Admission laboratory values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean glucose, mg/dL</td>
<td>219.5±104.7</td>
<td>242.3±120.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypoglycemia, glucose &lt;70 mg/dL</td>
<td>2.0</td>
<td>1.8</td>
<td>0.63</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt;136 mg/dL</td>
<td>19.1</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>136–185 mg/dL</td>
<td>21.6</td>
<td>19.9</td>
<td></td>
</tr>
<tr>
<td>186–250 mg/dL</td>
<td>28.9</td>
<td>28.8</td>
<td></td>
</tr>
<tr>
<td>&gt;250 mg/dL</td>
<td>30.3</td>
<td>37.7</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Mortality

Overall mortality rate in the cohort was 7.4% at 30 days, 21.1% at 6 months, and 29.5% at 1 year. Compared with patients discharged on antihyperglycemic therapy, patients discharged off diabetic medications had significantly higher unadjusted mortality rates at all time points (13.6% versus 6.5% at 30 days, \(P<0.0001\); 29.0% versus 19.9% at 6 months, \(P<0.0001\); and 37.6% versus 28.2% at 1 year, \(P<0.0001\)). After multivariable adjustment, higher mortality rates persisted in the group discharged off medication at 30 days (hazard ratio [HR], 1.64; 95% confidence interval [CI], 1.35 to 1.99), 6 months (HR, 1.38; 95% CI, 1.21 to 1.58), and 1 year (HR, 1.29; 95% CI, 1.15 to 1.45) (see Table 2 and the Figure).

Readmissions

At 1 year, 64.0% of patients had at least one readmission for any cause, with 18.6% being readmitted for MI and 42.5% for heart failure. Compared with patients discharged on therapy, those discharged off diabetic medications had similar crude readmission rates for all causes at 30 days (25.0% versus 25.5%, \(P=0.68\)) and at 6 months (51.7% versus 53.8%, \(P=0.19\)) but lower rates at 1 year (61.0% versus 64.5%, \(P=0.11\)).

### Table 1. One-Year Mortality Rates and Readmissions for Unadjusted and Multivariable Analyses

<table>
<thead>
<tr>
<th>Unadjusted Analysis</th>
<th>Hazard Risk</th>
<th>(P) Value</th>
<th>Multivariable Analysis</th>
<th>Hazard Risk</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1.47 (1.32–1.64)</td>
<td>(&lt;0.001)</td>
<td>1.29 (1.15–1.45)</td>
<td>(&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>MI readmission</td>
<td>0.80 (0.69–0.93)</td>
<td>0.004</td>
<td>0.91 (0.77–1.06)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.96 (0.87–1.06)</td>
<td>0.42</td>
<td>0.95 (0.85–1.05)</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>All-cause readmission</td>
<td>0.93 (0.86–1.00)</td>
<td>0.06</td>
<td>0.95 (0.87–1.03)</td>
<td>0.19</td>
<td></td>
</tr>
</tbody>
</table>

Hazard risks calculated for those discharged off versus those discharged on antihyperglycemic agents.
Readmission rates for AMI were similar at 30 days (4.4% versus 5.2%, \( P = 0.27 \)) but lower at 6 months (11.4% versus 14.4%, \( P = 0.005 \)) and at 1 year (15.6% versus 19.1%, \( P = 0.005 \)) for those discharged off antihyperglycemia therapy. There were no differences in readmissions for heart failure at any time point.

After multivariable adjustment, the risks for readmission for MI (HR, 0.91; 95% CI, 0.77 to 1.06), heart failure (HR, 0.95; 95% CI, 0.85 to 1.05), and all causes (HR, 0.95; 95% CI, 0.87 to 1.03) at 1 year were not significantly different among those discharged off versus on antihyperglycemic medications.

**Stratified Analyses**

Stratified analyses of patients based on discharge disposition were performed because of concerns that discharge to an intermediate/long-term care facility may reflect the reluctance to continue antihyperglycemic therapy in sicker patients with multiple coexisting illnesses. After multivariable adjustment, 1-year mortality hazard ratio for those discharged off diabetic medications was higher among those discharged to home (HR, 1.22; 95% CI, 1.04 to 1.42, \( P = 0.02 \)) and for those discharged to intermediate/long-term care facilities (HR, 1.35; 95% CI, 1.11 to 1.65, \( P = 0.003 \); interaction \( P = 0.19 \)).

Readmission rates to acute care facilities were not significantly different, based on the discharge regimen in either stratum.

Further stratified analyses showed higher 1-year mortality rates for those patients discharged off glucose lowering medications who had preserved LV systolic function (HR, 1.53; 95% CI, 1.24 to 1.90; interaction \( P = 0.55 \)), who did not have heart failure or edema on admission chest radiography (HR, 1.41; 95% CI, 1.21 to 1.64; interaction \( P = 0.02 \)), and who did not undergo any revascularization procedure during their hospital stay (HR, 1.28; 95% CI, 1.13 to 1.45; interaction \( P = 0.75 \)).

**Discussion**

In the present retrospective observational study of a large nationally representative sample of older patients with diabetes hospitalized for AMI, glucose-lowering therapy present on admission was not continued or resumed in 13.4% of patients on discharge. This was associated with a 47% higher risk for 1-year mortality in the unadjusted analysis. Even more pronounced higher mortality risk was present at 30 days and at 6 months in those discharged off diabetic medications, suggesting the possibility that discontinuation of antihyperglycemic therapy may preferentially impact early death in this setting. The higher mortality rates persisted after multivariable adjustment for a multitude of patient, hospital, and physician characteristics, the increased hazard risk being attenuated only modestly to 29%.

In contrast to higher mortality rates, hospital readmissions (including for recurrent AMI) did not differ between those discharged on versus off diabetic medications in the multivariable models. There are several possible explanations as to why hospitalization rates did not parallel increased mortality. First, this may be the result of censoring deaths in the model (higher mortality in the group off diabetic medications resulting in fewer opportunities for readmission). Second, this pattern may suggest increased rates of out-of-hospital deaths (including, potentially, sudden deaths) in the untreated group. Third, other factors associated with discontinuation of antihyperglycemic therapy, such as medical futility, multiple comorbidities, and even patient choice, may influence the decision to readmit.

Stratified analyses based on discharge disposition status were performed because of the possibility that a patient’s clinical status and prognosis may largely influence the decision to address glycemia after hospitalization. Patients requiring intermediate/long-term care after their acute hospitalizations may, for those reasons, be prescribed drug therapy for their diabetes less often. After adjustments, however, we found an increased mortality hazard risk in those discharged off glucose-lowering therapy, irrespective of discharge disposition to home or to an intermediate/long-term care facility.

Although we could not assess glycemic control in our patients nor the resumption of antihyperglycemic therapy after discharge, greater degrees of hyperglycemia expected in the off diabetes medication group could have several adverse physiological consequences for the recovering myocardium. Prior studies have shown that higher glucose levels in the setting of AMI are associated with higher free fatty acid
concentrations, which, in turn, may result in increased myocardial oxygen consumption, reduced myocardial contractility, and increased risk for arrhythmias. In addition, hyperglycemia at the time of AMI has been associated with enhanced thrombin generation, platelet activation, endothelial dysfunction, and well as vascular inflammation, each of which may plausibly contribute adversely to prognosis during the early recuperative period. Conceivably, the inappropriate discontinuation of antihyperglycemic therapy after AMI may potentiate further tissue injury to an already vulnerable myocardium in these individuals. Alternatively, our findings may, at least in part, reflect unmeasured confounding effects of multiple factors contributing to the discontinuation of glucose-lowering therapy in a subset of patients. Certainly, the decision to discontinue such agents in sicker patients with poorer prognosis and multiple comorbidities could contribute to the differences in mortality between the 2 groups. We attempted to minimize confounding by performing multivariable adjustment for multiple comorbidities. In addition, stratified analyses demonstrate persistent risks associated with the discontinuation of glucose-lowering therapy in patients with preserved systolic function as well as those discharged to home, that is, those with, ostensibly, the best prognosis.

Several recent trials have addressed the long-term effects of glycemic control on cardiovascular complications in patients with type 2 diabetes. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, intensive glucose control with resultant glycohemoglobin (HbA1c) of 6.5% was compared with standard therapy with resultant HbA1c of 7.2% had no significant effects on major macrovascular events, death from cardiovascular causes, or all-cause mortality. Similarly, in the Action to Control Cardiovascular Risk in Diabetes Study (ACCORD), intensive glycemic control (resultant HbA1c of 6.4% versus 7.5% in the conventional care arm) over 3.5 years did not significantly reduce combined macrovascular events (nonfatal MI, nonfatal stroke, and death from cardiovascular causes). There was a significant reduction in the risk for nonfatal MI in the intensively treated group but also a surprising (and to date unexplained) increase in all-cause mortality. In the Veterans Administration Diabetes Trial (VADT), macrovascular event rates after median follow-up of 5.6 years did not differ between groups despite marked differences in glycemic control (HbA1c of 6.9% versus 8.4% in the intensive and conventional care arms, respectively) superimposed on meticulous control of other cardiovascular risk factors. These trials have raised doubts regarding the efficacy of intensive glycemic control for prevention of future cardiovascular events, particularly in those patients with established macrovascular disease. As a result, a recent position statement from the American Diabetes Association, American Heart Association, and the American College of Cardiology endorses less stringent HbA1c goals for those patients with multiple comorbid conditions, established macrovascular disease, and limited life expectancy.

In the context of the above trial data and recommendations, how do we interpret our observations of significant mortality differences over the relatively short follow-up period between groups of older AMI patients discharged on versus off glucose-lowering medications? Although the above 3 trials were enriched (about one third) with patients with overt macrovascular disease, they were not designed to specifically evaluate glycemic control immediately after major coronary events. As previously noted, the hyperglycemic milieu following AMI may be particularly toxic to the recently injured, recovering, and organizing myocardium. Accordingly, the influence of glycemic control during this vulnerable time period may be uniquely important. In addition, our study contained a much older and a generally sicker population, with multiple comorbidities and very high overall mortality rates; the effects of hyperglycemia (and the proposed benefits from its treatment) may therefore be more pronounced here. We were also not able to evaluate glycemic control per se but used discharge medication prescription as a surrogate. Therefore, it is possible that our 2 groups had much greater differences in their glycemic indices than those studied in the controlled clinical trials.

Nonetheless, our data argue against the complete abandonment of antihyperglycemic therapy in older patients with recent AMI. Moreover, they suggest that although long-term glycemic control may have little effect on the prevention of future cardiovascular events, the use of antihyperglycemic therapy after AMI may need to be considered separately. Certainly, the reasons for the failure to resume antihyperglycemic therapy in a significant proportion of patients with diabetes after AMI must be better understood. In addition, further investigation of the relationship between glycemic control after AMI and patient outcomes appears warranted.

To our knowledge, our retrospective study is the first large investigation into the effects of discontinuation of antihyperglycemic therapy after AMI. Yet, there are several limitations to consider when interpreting our data. As mentioned, because of the observational design of our study, unmeasured confounding factors could influence our observed associations. Our database captures medications prescribed on discharge, but it was not possible to determine compliance or changes in drug regimen nor to track the quality of blood glucose control in the follow-up period. (However, such misclassification would tend to bias the study toward the null hypothesis.) We were also not able to determine the reasons for the discontinuation of antihyperglycemic medications in our study, and it is possible that there were new contraindications to therapy. Although rates of hypoglycemia on admission, which might have led to discontinuation of the medications, did not differ between the groups (=2.0%), in-hospital hypoglycemic episodes after admission could not be ascertained. Hypoglycemia in the setting of acute MI has indeed been associated with adverse outcomes. Much lower rates of prescription of cardiac medication in the group discharged off antihyperglycemic therapy (although adjusted for in our multivariable models), might also suggest that hospital-system factors may affect patient outcomes. Our additional controlling for hospital region and type (ie, teaching versus nonteaching) may not have fully accounted for this possibility. We were also not able to exclude patients with type 1 diabetes, although it is unlikely that they represented
more than a small minority of the older Medicare population in our study. Finally, because this study only analyzed data from older Medicare beneficiaries discharged from hospitals after AMI, the results may not apply to other patient populations, such as younger individuals or those with chronic, stable coronary artery disease, or to those with higher rates of utilization of evidence-based therapies (β-blockers, ACE inhibitors). These limitations require careful consideration. Furthermore, the outcomes associated with the discontinuation of antihyperglycemic therapy should be explored in additional databases, preferably in those in which it might be possible to determine the reason why medications were not continued or resumed on discharge.

In conclusion, the present study suggests that failure to continue (or resume) antihyperglycemic therapy in older patients with diabetes after discharge for AMI is associated with higher mortality within the first year. Although it is unclear whether this represents the effects of uncontrolled hyperglycemia after discharge, because quality of glucose control could not be evaluated in our study, maintaining patients on some regimen for their diabetes may be important in preventing adverse clinical outcomes. Future studies evaluating the reasons behind discontinuation of antihyperglycemic therapy, as well as specific effects of glyemic treatment after AMI are needed to identify opportunities to optimize clinical outcomes in this high-risk group of patients with coexisting diabetes and coronary artery disease.

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Disclosures

Dr Kosiborod is a member of the Advisory Board for Sanofi Aventis. Dr Masoudi is a member of the advisory board for Amgen and has contracts with the American College of Cardiology, the Oklahoma Foundation for Medical Quality, and Axio Research. Dr Krumholz is chair of the Scientific Advisory Board for UnitedHealthcare. Dr Inzucchi is consultant/advisor for Takeda, Merck, Amylin, Daiichi-Sankyo, and Medtronic, speaker for Novo Nordisk, and recipient of a research grant from Eli Lilly.

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Résumés d’articles

Conséquences cliniques de l’interruption du traitement hypoglycémiant après un infarctus aigu du myocarde chez le diabétique âgé

Kasia J. Lipska, MD ; Yongfei Wang, MS ; Mikhail Kosiborod, MD ; Frederick A. Masoudi, MD, MSPH ; Edward P. Havranek, MD ; Harlan M. Krumholz, MD, SM ; Silvio E. Inzucchi, MD

Contexte—Il est fréquent qu’un patient diabétique soit hospitalisé pour un infarctus myocardique aigu (IMA) alors qu’il suit un traitement hypoglycémiant et qu’il quitte ensuite l’hôpital sans prescription de ce type. Nous avons cherché à déterminer la fréquence de cette pratique ainsi que ses conséquences cliniques en termes de réhospitalisation et de mortalité.

Méthodes et résultats—Nous avons mené une étude prospective sur 24 953 diabétiques affiliés à Medicare qui avaient été hospitalisés pour un IMA et étaient ensuite rentrés chez eux. Nous avons évalué la fréquence des arrêts du traitement hypoglycémiant à la sortie d’hôpital chez les patients qui en suivaient un à leur arrivée. Nous avons, par ailleurs, utilisé des modèles de risques proportionnels multivariés de Cox ajustés en fonction du patient, du médecin et des variables hospitalières pour établir le lien indépendant existant entre la sortie d’hôpital et le traitement hypoglycémiant. Nous avons ensuite analysé les relations de ces variables avec les événements de mortalité et de réhospitalisation sur une période de 1 an. Parmi les patients qui prenaient au moins un médicament hypoglycémiant lors de leur admission, 8 751 satisfaisaient à nos critères d’inclusion et d’exclusion. Parmi eux, 7 581 (86,6 %) sont sortis avec un traitement hypoglycémiant et 1 170 (13,4 %) sans prescription de ce type. L’analyse multivariée a révélé que, par rapport aux patients qui avaient continué à être traités pour leur diabète à la sortie d’hôpital, ceux auxquels aucun traitement hypoglycémiant n’avait été prescrit avaient présenté un taux de mortalité plus élevé à un an (risque relatif : 1,29 ; intervalle de confiance [IC] à 95 % : 1,15 à 1,45). En revanche, les taux de réhospitalisations n’ont pas significativement différé d’un groupe à l’autre (risque relatif : 0,95 ; IC à 95 % : 0,87 à 1,03).


Mots clés : infarctus du myocarde aigu ■ diabète ■ traitement hypoglycémiant ■ sortie d’hôpital

Contribution de trente biomarqueurs à l’estimation du risque cardiovasculaire à dix ans dans deux cohortes de populations

Le programme MORGAM (MONICA, Risk, Genetics, Archiving, and Monograph) d’évaluation des biomarqueurs

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Contexte—L’estimation du risque cardiovasculaire au moyen des biomarqueurs nouvellement identifiés demande à être réalisée au sein de cohortes de sujets sains faisant l’objet d’un suivi afin de recenser les événements cardiovasculaires survenus depuis l’inclusion, en s’appuyant pour cela sur l’analyse des échantillons sériques et plasmatiques archivés à l’entrée dans l’étude. Nous rapportons ici les données recueillies dans deux cohortes ayant donné lieu à une telle étude en continu.

Méthodes et résultats—Chez 7 915 hommes et femmes de la cohorte de population FINRISK97 dans laquelle 538 événements cardiovasculaires s’étaient produits sur une période de 10 ans (événements coronaires ou cérébrovasculaires fataux ou non), nous avons évalué 30 marqueurs biologiques nouveaux intervenant dans des voies physiopathologiques distinctes, ce qui nous a