The cardiovascular metabolic syndrome
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Effect of Diabetes Mellitus and its Treatment on Ventricular Arrhythmias Complicating Acute Myocardial Infarction

Abstract

Aims:
To evaluate the effect of diabetes mellitus and its treatment on the risk of arrhythmias among early survivors of acute myocardial infarction.

Research design and method:
The Onset Study was conducted in 64 U.S. medical centers. Between August 1989 and September 1996, 3882 patients were interviewed after having an acute myocardial infarction. We used logistic regression models to examine the association of diabetes mellitus and its treatment with the risk of ventricular arrhythmia after adjustment for age, gender, hypertension, thrombolytic therapy, smoking, obesity, cardiac medicines and congestive heart failure.

Results:
During the index hospitalization, patients with diabetes (n=814) were less likely to develop ventricular arrhythmias than patients without diabetes (6.8 vs. 13.3%, p<0.001). The risk of ventricular arrhythmia in patients treated with first generation sulfonylureas or diet alone was similar to patients without diabetes (OR = 0.91; 95% CI, 0.39-2.15, and 0.76; 95% CI, 0.46-1.26, respectively). However, compared to patients without diabetes, the adjusted odds ratio (OR) for ventricular arrhythmias was lower among patients treated with insulin or patients treated with second generation sulfonylureas (OR= 0.54, 95% CI 0.32-0.92; OR= 0.45,95% CI 0.27-0.75, respectively).

Conclusions:
Compared to patients without diabetes, the risk of ventricular arrhythmias complicating acute myocardial infarction is lower in patients with diabetes treated with second generation sulfonylureas or insulin, but not in those treated with first generation sulfonylureas or diet alone. This suggests that differences in the mechanism of action of different sulfonylureas may result in clinically relevant differences in arrhythmic risk.
Introduction

Acute Myocardial Infarction (MI) is a major cause of morbidity and mortality among patients with diabetes. Moreover, the prognosis of patients with acute MI is worse among patients with diabetes than among patients without diabetes (1,2). Whether the type of treatment for diabetes influences the short-term outcome of acute MI is uncertain. There are conflicting reports on the effect of the type of diabetes therapy on mortality and complications following acute MI among patients with diabetes (3, 4,5,6).

The frequency of ventricular arrhythmias complicating acute MI among patients with diabetes mellitus treated with oral hypoglycemic agents has been reported to be no different (7) or lower (8) than the frequency in patients free of diabetes. Reports regarding effects of oral agents on frequency of arrhythmias in animal models are also divergent (9,10). Moreover a recent study showed that risk of ventricular arrhythmias was lower in patients with decompensated heart failure with diabetes (11). However that study did not investigate a potential differential effect of type of therapy used to treat diabetes.

To evaluate this further, we studied early survivors of acute MI, and compared the incidence of ventricular arrhythmias complicating acute MI among patients with diabetes treated with first generation sulfonylureas, second generation sulfonylureas, insulin, diet alone and among patients free of diabetes who were enrolled in the determinants of myocardial infarction onset study (12).

Study subjects and methods

The design of the Onset Study has been previously reported (12) and is described here in brief. Between August 1989 and September 1996, 3882 patients (1258 women and 2624 men) were interviewed at 64 medical centers in United States, a median of 4 days (range 0 to 30) after having an acute MI.
Trained research interviewers identified eligible patients by reviewing coronary care unit admission logs and patient charts. For inclusion, patients were required to have a creatine kinase (CK) level above the upper limit of normal for each center, positive CK-MB isoenzymes, an identifiable onset of symptoms typical of infarction, and the ability to complete a structured interview. The institutional review board of each center approved this protocol, and interviewers obtained informed consent from each patient.

Interviewers used a structured data abstraction and questionnaire form. Information collected from each interview and chart review included patient age, sex, medical history, and medication use (both prescription and nonprescription). All participants were asked to describe the specific symptoms that characterized the infarction.

We defined diabetes as a history of diabetes obtained during chart review or the current use of any hypoglycemic medication. We categorized the type of treatment for diabetes as diet alone, use of oral hypoglycemics and insulin therapy as documented in the patient’s medical records. We further divided oral hypoglycemics into first generation sulfonylureas (Tolbutamide, Tolazamide, Acetohexamide and Chlorpropamide), second generation sulfonylureas (Glyburide and Glipizide) and metformin.

Interviewers used a structured data abstraction and questionnaire form and were instructed to collect all electrocardiographic interpretations (n = 2422) available at the time of the interview. Only final electrocardiographic interpretations by local electrocardiographers were used, and the criteria for determination of Q-wave infarction were not standardized. During the chart review, interviewers also recorded complications from an established list (CHF, cardiac arrest, shock, ventricular tachycardia or fibrillation, atrial fibrillation, hypotension, stroke, or atrioventricular block). These diagnoses were recorded only if treating clinicians documented the presence of these complications in the medical record. The outcomes considered for ventricular arrhythmias, were ventricular fibrillation (VF) and ventricular tachycardia (VT), and arrhythmias occurring from the time of acute MI up to the time of interview were recorded. Current aspirin use was defined as the reported use of any aspirin or aspirin-containing product in the 4 days before onset of the index myocardial infarction.
Previous coronary artery disease was defined as any report of a previous myocardial infarction or angina pectoris noted during patient interview or chart review.

We analyzed continuous and binary variables using Student’s $t$ tests and Fisher’s exact tests, respectively. We used logistic regression models to examine the effect of diabetes and its treatment on the odds of arrhythmias after adjustment for potentially confounding factors. The factors we included were age, gender, hypertension, thrombolytic therapy, smoking, obesity, digoxin, regular use of aspirin, calcium channel blockers, beta blockers, and ACE Inhibitors and congestive heart failure at baseline.

To ensure that our results were robust, we repeated our regression analysis using stepwise models with entry and stay criterion of 0.2. We present odds ratios (ORs) from logistic regression models with their 95% confidence intervals (CI). All probability values presented are two-sided.

Results

The characteristics of the Onset Study patients have been reported previously (2) and are shown in Table 1. Patients with diabetes were generally older and more likely to be women, obese and sedentary. They had more comorbidity and used cardiac medication more frequently. They were less likely to be white or to be current smokers, and they reported lower educational attainment. There was no difference between patients with and without diabetes in time to interview (mean difference between groups 0.17 days; $p=0.32$). During the index hospitalization, patients with diabetes were twice as likely to develop congestive heart failure as were patients without diabetes (RR 1.9; 95% CI 1.6-2.2).

Of the 814 patients with diabetes, 192 were on a restricted diet only, 250 were on insulin, 384 were on oral antidiabetic agents including 62 treated with first generation sulfonylureas, 313 with second generation sulfonylureas, 1 patient took metformin and 8 patients did not specify the medication. Among the insulin-treated patients,
there were 12 who also taking a second generation sulfonylureas and one was additionally on metformin. Among patients with diabetes, there was no difference in time to interview by treatment type (p=0.16). In general differences in clinical characteristics across treatment type were small (Table 2).

There were 462 cases of ventricular arrhythmias, including 368 cases of VT alone, 81 cases of VF alone, and 13 cases with both VT and VF. Table 3 shows that patients

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### Table 1 – Characteristics of Onset Study Patients According to History of Diabetes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Diabetes (n=814)</th>
<th>No diabetes (n=3068)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.7 ±11.5</td>
<td>60.6 ±12.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Female</td>
<td>356 (44%)</td>
<td>902 (29%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>White race</td>
<td>649 (81%)</td>
<td>2694 (89%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 ±5.6</td>
<td>26.9 ±4.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>171 (21%)</td>
<td>1109 (36%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Former smoker</td>
<td>353 (44%)</td>
<td>1200 (39%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Obese (&gt; 29 kg/m²)</td>
<td>355 (44%)</td>
<td>882 (29%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No Exertion</td>
<td>698 (86%)</td>
<td>2292 (75%)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

**Education**
- Less than high school | 214 (27%) | 626 (21%) | <.0001 |
- Complete High school | 350 (44%) | 1238 (41%) | |
- Some college | 236 (29%) | 1136 (38%) | |

**Regular Use of Medication**
- Aspirin | 321 (39%) | 1136 (37%) | 0.21 |
- Ca Blockers | 289 (35%) | 638 (21%) | <.0001 |
- Digoxin | 85 (10%) | 171 (6%) | <.0001 |
- B- Blockers | 189 (23%) | 644 (21%) | 0.18 |
- ACE Inhibitors | 185 (23%) | 330 (11%) | <.0001 |

**Past Cardiac History**
- Previous MI | 284 (35%) | 743 (25%) | <.0001 |
- Angina | 261 (32%) | 689 (23%) | <.0001 |
- Hypertension | 476 (58%) | 1220 (40%) | <.0001 |
- CHF - Baseline | 31 (4%) | 54 (2%) | 0.001 |

**Characteristics of Index Hospitalization**
- CHF | 173 (21%) | 344 (11%) | <.0001 |
- Q-wave Infarction | 252 (51%) | 1126 (58%) | 0.002 |
- Thrombolytic Therapy | 258 (32%) | 1291 (42%) | <.0001 |

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**Notes:**
- **a** Missing data; 39 patients for race, 40 patients for BMI, 32 patients for smoking status, 73 patients for previous MI, 82 patients for education, 1460 for Q-wave infarction. **b** Physical exertion ≥6 METs less than once weekly. **c** METs= metabolic equivalents; **AC E** = angiotensin-converting enzyme; **BMI** = body mass index; **CH F** = congestive heart failure; **VT** = ventricular tachycardia; **MET** = metabolic equivalent.
**Diabetes Mellitus and Ventricular Arrhythmias**

**Table 2 – Characteristics of Patients with Diabetes According to Type of Therapy.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Diet (n=192)</th>
<th>1st Generation SU's (n=62)</th>
<th>2nd Generation SU's (n=313)</th>
<th>Insulin (n=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.3±11.6</td>
<td>69.7±8.7</td>
<td>64.8±10.6</td>
<td>63±12</td>
</tr>
<tr>
<td>Female</td>
<td>70 (37%)</td>
<td>29 (47%)</td>
<td>132 (42%)</td>
<td>127 (51%)</td>
</tr>
<tr>
<td>White race</td>
<td>148 (78%)</td>
<td>51 (85%)</td>
<td>257 (83%)</td>
<td>196 (79%)</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>44 (23%)</td>
<td>12 (20%)</td>
<td>73 (24%)</td>
<td>45 (18%)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>93 (48%)</td>
<td>28 (45%)</td>
<td>128 (41%)</td>
<td>105 (42%)</td>
</tr>
<tr>
<td>Obese (&gt; 29 kg/m²)</td>
<td>77 (40%)</td>
<td>18 (29%)</td>
<td>147 (48%)</td>
<td>114 (46%)</td>
</tr>
<tr>
<td>No Exertion</td>
<td>166 (86%)</td>
<td>56 (90%)</td>
<td>265 (85%)</td>
<td>208 (83%)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>48 (25%)</td>
<td>19 (31%)</td>
<td>75 (24%)</td>
<td>73 (30%)</td>
</tr>
<tr>
<td>Complete High school</td>
<td>82 (43%)</td>
<td>26 (43%)</td>
<td>140 (45%)</td>
<td>106 (44%)</td>
</tr>
<tr>
<td>Some College</td>
<td>59 (31%)</td>
<td>16 (28%)</td>
<td>96 (31%)</td>
<td>64 (26%)</td>
</tr>
<tr>
<td>Regular Use of Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>89 (46%)</td>
<td>27 (44%)</td>
<td>118 (38%)</td>
<td>91 (36%)</td>
</tr>
<tr>
<td>Ca Blockers</td>
<td>69 (36%)</td>
<td>19 (31%)</td>
<td>116 (37%)</td>
<td>90 (36%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>28 (14%)</td>
<td>6 (10%)</td>
<td>26 (8%)</td>
<td>25 (10%)</td>
</tr>
<tr>
<td>B- Blockers</td>
<td>35 (18%)</td>
<td>19 (31%)</td>
<td>83 (27%)</td>
<td>56 (22%)</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>52 (27%)</td>
<td>8 (13%)</td>
<td>64 (20%)</td>
<td>63 (25%)</td>
</tr>
<tr>
<td>Past Cardiac History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>123 (65%)</td>
<td>38 (62%)</td>
<td>211 (69%)</td>
<td>144 (58%)</td>
</tr>
<tr>
<td>Angina</td>
<td>72 (37%)</td>
<td>16 (26%)</td>
<td>86 (27%)</td>
<td>89 (36%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>115 (60%)</td>
<td>38 (61%)</td>
<td>182 (58%)</td>
<td>143 (57%)</td>
</tr>
<tr>
<td>CHF - Baseline</td>
<td>7 (4%)</td>
<td>2 (3%)</td>
<td>7 (2%)</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>Characteristics of Index Hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>42 (22%)</td>
<td>12 (19%)</td>
<td>67 (21%)</td>
<td>52 (21%)</td>
</tr>
<tr>
<td>Q-wave Infarction</td>
<td>54 (45%)</td>
<td>15 (45%)</td>
<td>110 (55%)</td>
<td>73 (48%)</td>
</tr>
<tr>
<td>Thrombolytic Therapy</td>
<td>64 (33%)</td>
<td>14 (23%)</td>
<td>104 (33%)</td>
<td>72 (29%)</td>
</tr>
</tbody>
</table>

*Missing data; 39 patients for race, 40 patients for BMI, 32 patients for smoking status, 73 patients for previous MI, 82 patients for education, 1460 for Q-wave infarction. Physical exertion ≥ 6 METs less than once weekly. 1st Generation Sulfonylureas include Tolbutamide, Tolazamide, Acetohexamide and Chlorpropamide. 2nd Generation Sulfonylureas include Glyburide, Glipizide. METs = metabolic equivalents; ACE = angiotensin-converting enzyme; BMI = body mass index; CHF = congestive heart failure; VT = ventricular tachycardia; MET = metabolic equivalent.

With diabetes (n=814) had a lower frequency of ventricular arrhythmias than patients without diabetes (6.8% versus 13.3%, p-value < .001). In the multivariate analysis, the odds of sustaining a ventricular arrhythmia complicating acute MI were significantly lower among patients with diabetes compared with that for patients free of diabetes (odds ratio = 0.55, 95% CI 0.40-0.74).
Table 3. Ventricular Arrhythmias Associated with Diabetes and its Type of Therapy.

<table>
<thead>
<tr>
<th></th>
<th>Ventricular Tachycardia (%)</th>
<th>Ventricular Fibrillation (%)</th>
<th>Ventricular Arrhythmias&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>Adjusted odds ratio for VA (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Diabetes (n=3068)</td>
<td>330 (10.8%)</td>
<td>90 (2.9%)</td>
<td>407 (13.3%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diabetes (n=814)</td>
<td>51 (6.3%)</td>
<td>4 (0.5%)</td>
<td>55 (6.8%)</td>
<td>0.55 (0.40-0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diet (n=192)</td>
<td>18 (9.4%)</td>
<td>0 (0%)</td>
<td>18 (9.4%)</td>
<td>0.76 (0.46-1.26)</td>
<td>0.29</td>
</tr>
<tr>
<td>Insulin (n=250)</td>
<td>13 (5.2%)</td>
<td>3 (1.2%)</td>
<td>16 (6.4%)</td>
<td>0.54 (0.32-0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Generation SUs&lt;sup&gt;c&lt;/sup&gt; (n=62)</td>
<td>5 (8.1%)</td>
<td>1 (1.6%)</td>
<td>6 (9.7%)</td>
<td>0.91 (0.39-2.15)</td>
<td>0.83</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Generation SUs&lt;sup&gt;d&lt;/sup&gt; (n=313)</td>
<td>17 (5.4%)</td>
<td>0 (0%)</td>
<td>17 (5.4%)</td>
<td>0.45 (0.27-0.75)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<sup>a</sup> 13 participants had both VT and VF; counted once for total ventricular arrhythmias. <sup>b</sup> Adjusted for age (as a continuous variable), gender, hypertension, thrombolytic therapy, current smoking, obesity, regular use of digoxin, aspirin, calcium channel blocker, beta-blocker, ACE inhibitor and congestive heart failure at baseline. <sup>c</sup> 1<sup>st</sup> Generation Sulfonylureas include Tolbutamide, Tolazamide, Acetohexamide and Chlorpropamide. <sup>d</sup> 2<sup>nd</sup> Generation Sulfonylureas include Glyburide, Glipizide.

Further adjustment for Q-wave infarction (2422 subjects) did not alter the lower risk of ventricular arrhythmias among patients with diabetes (odds ratio=0.58, 95% CI 0.40-0.85). Adjusting for time to interview also did not alter the results materially (odds ratio=0.54, 95% CI 0.39-0.74). After, additionally adjusting for noncardiac comorbidity, race, education, and exertion, the odds of sustaining a ventricular arrhythmia complicating acute MI remained lower among patients with diabetes (odds ratio=0.58, 95% CI 0.42-0.79).

Table 3 also shows that compared to patients free of diabetes, the odds of ventricular arrhythmias complicating acute MI was significantly lower among patients with diabetes who were treated with second generation sulfonylureas or insulin (odds ratio = 0.45, 95% CI 0.27-0.75; odds ratio = 0.54, 95% CI 0.32-0.92, respectively). However, there was no significant difference in the estimated odds of ventricular arrhythmias among patients treated with either first generation sulfonylureas or diet alone compared to subjects free of diabetes.

Among all subjects on oral agents, the average date of onset of MI for those on first generation sulfonylureas was 397 days earlier than for patients with diabetes not on these agents (p<0.001). Although, those on first generation sulfonylureas were somewhat less likely to receive thrombolytic therapy, this difference was not statistically significant.
Diabetes Mellitus and Ventricular Arrhythmias

(odds ratio adjusted for age and sex = 0.7, 95% CI 0.4-1.4) than those patients with diabetes not on first generation sulfonylureas. Importantly, adjusting for the date of the index MI did not materially alter our findings. Likewise, additional adjustment for noncardiac comorbidity, race, education, and exertion did not change our results.

Sensitivity Analysis
We performed sensitivity analyses to ensure that our results were robust. Repeating the multivariable analyses using stepwise logistic regression to select the covariates to remain in the model did not materially alter any of the results. The odds ratio for ventricular arrhythmias complicating acute MI among patients with diabetes compared to those free of diabetes was similar among subgroups of patients with and without a history of hypertension, cigarette smoking and obesity. However, the lower odds of ventricular arrhythmias associated with diabetes was somewhat more pronounced among women than men, with an odds ratio of 0.39, 95% CI 0.22-0.71 among women and 0.69, 95% CI 0.48-1.00 among men (p=0.06 for interaction).

Discussion
In this analysis of patients enrolled in Onset Study, we found that compared to patients without diabetes, the odds of ventricular arrhythmias complicating acute MI is lower among patients with diabetes treated with second generation sulfonylureas or insulin, but not among those treated with first generation sulfonylureas or diet alone. These results were robust and remained significant after multivariable adjustment. The incidence of ventricular arrhythmias (VT or VF) is known to be higher with Q-wave or ST segment elevation MI than non-Q wave infarctions (13, 14). In our study, there were more Q-wave infarctions among patients without diabetes. However even after adjusting for Q-wave infarction, patients with diabetes still had statistically significant lower odds of sustaining ventricular arrhythmias than patients free of diabetes.

Our results are consistent with those of Aronson et al. who reported that patients with diabetes had a lower risk of developing ventricular arrhythmias complicating
treatment of decompensated heart failure than patients without diabetes (11). Furthermore, in the GUSTO I (13) and GUSTO III (15) trials, patients with diabetes had a lower crude risk of ventricular arrhythmias than patients free of diabetes, although the results did not reach statistical significance and a multivariable analysis of other risk factors for ventricular arrhythmias was not presented.

Sulfonylureas and risk of ventricular arrhythmias

First and second generation sulfonylureas differ in some respects, for example, second generation agents have longer duration of action, form different metabolites after hepatic metabolism, and are 100 to 150 times more potent than first generation agents (16). Previous studies (4-9) have differed about whether treatment with sulfonylureas affects the outcome of patients with acute MI. For example Garratt et al. (4) reported that sulfonylurea treatment of patients with diabetes was associated with an increased risk of death among patients with MI treated with direct angioplasty. However they did not separately evaluate patients treated with first or second generation sulfonylureas. Moreover they did not find an increased risk of ventricular arrhythmias among patients treated with sulfonylureas. On the other hand, Lomuscia et al. (17) reported that the incidence of potentially lethal ventricular arrhythmias occurring in-hospital was lower among patients with diabetes, treated with second-generation sulfonylureas compared to patients without diabetes. In two other studies (7,18), second generation sulfonylureas were reported to be associated with a significantly lower incidence of ventricular arrhythmias during episodes of transient myocardial ischemia. Although the risk for ventricular arrhythmias among patient with diabetes treated with first generation sulfonylureas was not significantly different than patients free of diabetes in our study. Our ability to compare arrhythmia risk between patients treated with first and second generation sulfonylureas directly was limited by a small number of subjects.

The specific mechanisms that could underlie our results are speculative. Sulfonylureas inhibit potassium efflux through adenosine triphosphate sensitive potassium channels (K-ATP channels) in pancreatic beta cells. Such channels have been found in other tissues, including cardiac myocytes and vascular smooth muscle cells. Sulfonylureas have been shown to inhibit post- infarct arrhythmias in both humans (19, 20) and
animal models (11,21,22) by inhibition of myocardial K-ATP channels. Such findings have been an impetus to explore the clinical potential of these agents as a novel approach to anti-arrhythmic therapy (22,23).

Inhibition of K-ATP channels by sulfonylureas, may decrease ischemic-preconditioning with potentially deleterious effects on the outcome of myocardial ischemia (24). However, the potential harmful effects of sulfonylureas on ischemic preconditioning, may be counterbalanced by potential anti-arrhythmic effects (25,26). Our data suggest that potential inhibition of ischemic preconditioning by sulfonylurea agents is not associated with clinically meaningful differences in short-term outcome after acute MI.

**Insulin and risk of ventricular arrhythmias**

Our results are consistent with the finding of Ulgen et al. who reported that insulin might be able to prevent ventricular arrhythmias in the early period of acute myocardial infarction (27). Other studies indicate that glucose-insulin-potassium (GIK) therapy may have an important role in reducing in-hospital mortality after acute myocardial infarction (28).

Increased utilization of free fatty acids (FFA) during ischemia causes accumulation of toxic FFA metabolites that may induce more membrane damage, provoke arrhythmias and exacerbate mechanical dysfunction (29). Insulin promotes glucose oxidation and may protect ischemic myocardial cells by reducing FFA concentration and making glucose more available as an energy substrate (30).

These potential benefits (increased glucose uptake and decreased circulating FFA levels) have been exploited clinically with the use of GIK infusions in the setting of myocardial infarction, which has been associated with a reduced risk of ventricular arrhythmias and congestive heart failure (31). Also GIK in acute myocardial infarction is associated with a significant reduction in mortality among patients with diabetes, particularly among those not previously treated with insulin (32). Muller et al. showed that insulin therapy significantly improved myocardial performance and contractility in rat hearts after prolonged ischemia (33). Furthermore, Sack et al. (34) has proposed a direct
myocardial cell survival effect of insulin therapy as an adjunct to reperfusion after acute coronary ischemia, independent of metabolic modulation.

Limitations
We interviewed early survivors of myocardial infarction, so we cannot determine the case-fatality rate of myocardial infarction for our patients. It is possible that patients with diabetes who developed arrhythmias early in the course of their infarction have a worse prognosis than patients without diabetes (35) that developed arrhythmias. If this occurred, then the lower prevalence of ventricular arrhythmias that we observed might be due to fewer patients with diabetes and arrhythmias surviving, to be enrolled in our study compared with patients without diabetes that developed arrhythmias. However, we observed the expected higher risk of CHF among patients with diabetes arguing against a healthy survivor effect. Nonetheless our results can be considered hypothesis generating and require confirmation.

Misclassification of the outcome is possible since the diagnosis of VT or VF was based on the clinical diagnosis of the treating clinician as recorded in the medical records and the timing of VA was not recorded. Such misclassification is unlikely to be differential with respect to diabetes or its treatment and thus would be expected to bias our findings towards observing no effect of diabetes or its treatment on the risk of ventricular arrhythmias complication acute MI.

We also relied on the clinical diagnosis of diabetes made by the treating clinicians in the medical record and by patient self-report. This approach may have misclassified patients with unrecognized diabetes. Such misclassification would tend to minimize the effect of diabetes, so the relative risks reported here might be overly conservative. Our patients were hospitalized before studies confirmed that intensive blood glucose control decreases mortality during and after acute MI among patients with diabetes (33) and we did not have data on the degree of glycemic control of the Onset Study patients. It is possible that some of the apparent benefit of insulin and second generation agents may be related to the better glycemic control, an interesting area for
future investigation. Our results may also not reflect such changes in the treatment of acute MI although the rate of VA complications has not necessarily changed (13).

We do not have specific data on autonomic neuropathy or QT dispersion among Onset Study patients. Some studies suggest that these factors are common among people diabetes (36) and may increase risk of VA (37). Likewise we do not have the long term mortality data for the whole Onset Study population. Such information would be useful to include in future studies.

Our study shows that compared to patients without diabetes, the prevalence of ventricular arrhythmias among early survivors of acute MI is lower in patients with diabetes treated with second generation sulfonylureas or insulin, but not in those treated with first generation sulfonylureas or diet alone. This suggests that differences in their mechanism of action may result in clinically relevant differences in arrhythmic risk. Our study indicates the need of future studies for this important but unresolved issue of treatment of patients with diabetes who sustain acute MI.

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