Myocardial Structure, Function, and Scar in Patients With Type 1 Diabetes Mellitus

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Background—We report relationships between cardiovascular disease risk factors and myocardial structure, function, and scar in patients with type 1 diabetes mellitus in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study.

Methods and Results—Cardiac magnetic resonance was obtained in 1017 patients with type 1 diabetes mellitus. Gadolinium cardiac magnetic resonance was also obtained in 741 patients. The mean age was 49±7 years; 52% were men; and mean duration of diabetes mellitus was 28±5 years. Associations of cardiovascular disease risk factors with cardiac magnetic resonance parameters were examined with linear and logistic regression models. History of macroalbuminuria was positively associated with left ventricular mass (by 14.8 g), leading to a significantly higher ratio of left ventricular mass to end-diastolic volume (by 8%). Mean hemoglobin A1c levels over the preceding 22 years were inversely associated with end-diastolic volume (~3.0 mL per unit mean hemoglobin A1c percent) and stroke volume (~2.3 mL per unit mean hemoglobin A1c percent) and positively related to the ratio of elevated left ventricular mass to end-diastolic volume (0.02 g/mL per unit). The overall prevalence of myocardial scar was 4.3% by cardiac magnetic resonance and 1.4% by clinical adjudication of myocardial infarction. Both mean hemoglobin A1c (odds ratio, 1.5 [95% confidence interval, 1.0–2.2] per unit) and macroalbuminuria (odds ratio, 3.5 [95% confidence interval, 1.2–9.9]) were significantly associated with myocardial scar and traditional cardiovascular disease risk factors.

Conclusions—In addition to traditional cardiovascular disease risk factors, elevated mean hemoglobin A1c and macroalbuminuria were significantly associated with alterations in left ventricular structure and function. The prevalence of myocardial scar was 4.3% in this subcohort of DCCT/EDIC participants with relatively preserved renal function.


Key Words: cardiovascular diseases • diabetes mellitus, type 1 • magnetic resonance imaging • risk factors

Type 1 diabetes mellitus is associated with an increased risk of cardiovascular disease (CVD) and a high mortality from premature coronary artery disease.1,2 Major predictors of CVD for patients with type 1 diabetes mellitus in the Pittsburgh Epidemiology and Diabetes Complications (EDC) Study3 and EURODIAB Insulin Dependent Diabetes Mellitus Complications study4 included duration of diabetes mellitus, hypertension, elevated lipids, smoking, inflammatory markers, and renal disease. The role of glycemic control on the risk of CVD has been disputed,3,5–8 although long-term studies of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) study cohort have shown an association of hemoglobin A1c (HbA1c) levels with several measures of atherosclerosis and with CVD events.9–11

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In addition to asymptomatic CVD events, patients with type 1 diabetes mellitus may have a propensity for asymptomatic myocardial infarction associated with diabetic autonomic...
neuropathy. Myocardial dysfunction and nonatherosclerotic myocardial damage, perhaps from microvascular disease, may also occur in patients with type 1 diabetes mellitus. Diabetic cardiomyopathy is associated with left ventricular (LV) hypertrophy, and myocardial dysfunction may result directly from diabetes mellitus in the absence of concomitant atherosclerosis and hypertension.

Cardiac magnetic resonance (CMR) imaging is the current reference standard for the assessment of cardiac structure, function, and myocardial scar (dense myocardial fibrosis). The EDIC study is the first large-scale cohort to use CMR to evaluate patients with type 1 diabetes mellitus. The aim of this report is to study the relationships of CVD risk factors and HbA1c levels with myocardial structure, function, and scar in patients with type 1 diabetes mellitus.

### Methods

#### Study Sample

The DCCT and the EDIC study have been described previously in detail. In brief, between 1983 and 1989, 1441 patients (age, 13–39 years) with type 1 diabetes mellitus were recruited to compare the effects of intensive insulin therapy with conventional therapy. At the baseline visit (1983–1989), all patients were free of a history of clinical CVD, hypertension, and hypercholesterolemia. DCCT participants were recruited into a primary prevention cohort (1–5 years of diabetes mellitus duration and no retinopathy or microalbuminuria at baseline) or into a secondary intervention cohort (1–15 years of duration, minimal to moderate retinopathy, and no more than 200 mg albuminuria per 24 hours at baseline).

The EDIC study began in 1994 and is an ongoing, prospective, observational follow-up of the DCCT cohort. A total of 1301 participants (94% of the surviving DCCT cohort) were active in EDIC during years 14 to 16 at the time of CMR (Figure 1). The study was approved by the institutional review boards of all participating centers, and all subjects gave written informed consent.

#### Study Procedures

During DCCT, participants underwent an annual medical history and physical examination, ECG, and laboratory testing for fasting lipid levels, serum creatinine, albumin excretion, and other risk factors for CVD. Glycohemoglobin values (HbA1c) were measured (in percent of total hemoglobin) quarterly during DCCT and annually during EDIC. During the EDIC follow-up study, lipid profile and urinary albumin excretion rate were measured in alternate years. Weighted mean laboratory values over the study duration were computed with weights proportional to the time interval between values owing to the differences in the intervals between visits during DCCT and EDIC.

Hypertension was defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medications. Hypercholesterolemia was defined as low-density lipoprotein levels ≥130 mg/dL or use of lipid-lowering medication. Alcohol use was self-reported and defined as consumption of an average of at least 1 alcoholic beverage (12 oz beer, 4 oz wine, or 1.5 oz hard liquor) per week in the past year. ECGs were obtained at baseline, at every 2 years during DCCT, at closeout of DCCT, and annually during EDIC; they were centrally read and classified with the revised Minnesota code.

#### Assessment of Clinical Myocardial Infarction Events and Other Diabetic Complications

All complications were cumulative from the beginning of DCCT to the present study except for neuropathy. CVD included clinical myocardial infarction (MI; nonfatal) or ECG-diagnosed silent MI. Medical records of participants, including ECG findings and cardiac enzyme levels, were submitted for adjudication to a committee masked to treatment group assignment, HbA1c, and glucose levels. Clinical MI events classified as definite are included in these analyses. Silent MIs were identified on the basis of serial changes in Minnesota codes among all available ECGs during DCCT/EDIC as reported previously. Retinopathy was defined as any proliferative diabetic retinopathy or worse. Nephropathy included sustained microalbuminuria, defined as urinary albumin excretion rate >30 mg/24 h at any 2 consecutive visits or end-stage renal disease, and macroalbuminuria, defined as albumin excretion rate >300 mg/24 h at any visit or end-stage renal disease. Neuropathy included cardiac...
autonomic neuropathy from autonomic nervous system testing and confirmed clinical neuropathy from nerve conduction testing at EDIC year 13 or 14.

**CMR Imaging**

CMR was performed with a uniform protocol at 27 centers between July 2007 and April 2009 with 1.5-T magnets, except for 1 center that had a 3-T magnet (Esprec or Avanto, Siemens Medical Systems, Erlangen, Germany; Intera, Philips Medical Systems, Best, the Netherlands; Signa, GE Medical Systems, Waukesha, WI). Study subjects who agreed to participate and who had an estimated glomerular filtration rate $\geq 60 \text{ mL/min}^{-1} \text{ m}^{-2}$, no history of dialysis or renal transplantation, or no known allergy to gadolinium also underwent gadolinium-enhanced CMR with a 0.15- to 0.20-mmol/kg dose of gadolinium-based contrast.

CMR studies were centrally evaluated by readers blinded to all other study data. LV mass, volumes, and functional parameters were determined with QMass software (version 6, Medis, Leiden, the Netherlands). A detailed explanation of CMR sequences and image analysis presented in the Methods section in the online-only Data Supplement.

Myocardial scar was defined as focal enhancement either in 2 adjacent short-axis images or in 1 short-axis image and a long-axis image at a corresponding location. Myocardial scars were classified as either ischemic (involving the subendocardium in a coronary artery distribution) or nonischemic (predominantly midwall or subepicardial location without subendocardial involvement in a noncoronary distribution). For quantitative analysis, myocardial scar areas were traced manually.

Reread of 100 CMR scans revealed an intraclass correlation range from 0.917 to 0.978 and the relative technical error of measurement from 3% to 5% (Table I in the online-only Data Supplement).

**Statistical Analysis**

Clinical characteristics of DCCT/EDIC participants, measured immediately before or at the time of CMR scan, are reported as mean±SD or percentage. Groups of subjects were compared by use of the Wilcoxon rank-sum tests for quantitative variables and $\chi^2$ tests for categorical variables. Differences between groups in rare outcomes were evaluated by a 2-sided Fisher exact test. The reliability of cardiac parameters was evaluated by intraclass correlation and relative technical error measurement.21

The association of CVD risk factors with LV structure and function was evaluated by use of multivariate linear regression models with machine type (Siemens versus Philips versus GE), age, sex, height, weight, current smoking, current alcohol use, mean systolic blood pressure (SBP), high-density lipoprotein, low-density lipoprotein, and HbA1c, and macroalbuminuria. Mean SBP was retained in the multivariate regression analyses because it had a stronger association than diastolic blood pressure. Additional analyses used the medication-adjusted mean SBP in which a value of 10 mm Hg was added to every SBP value obtained while a subject was taking antihypertensive medications. The Hochberg multiple testing approach was used to adjust the $P$ values for the covariate effects in each multivariate regression model.22,23

The adjusted differences in the risks of myocardial scar and their association with CVD risk factors and LV measures were evaluated with logistic regression models adjusted for age and sex, as appropriate, with 95% confidence intervals (CIs). All analyses were performed with SAS software (version 8.2; SAS Institute, Cary, NC). $P$ values $<0.05$ were considered statistically significant.

**Results**

**Study Population**

Of the 1301 DCCT/EDIC participants who were active during EDIC years 14 to 16, 1240 participants were screened for CMR; 1017 participants had diagnostic CMR and were included in the analysis (Figure 1). Of these, 755 (74%) were also examined with gadolinium-delayed enhancement CMR. Of 262 who did not receive gadolinium CMR, the majority (173, 66%) were excluded because of moderate or worse renal dysfunction, renal transplantation, or dialysis (Figure 1). The mean age of included participants was 49 years; 48% of them were female; and their mean duration of diabetes mellitus was 28 years. The cardiovascular risk profile of participants who underwent CMR was similar to that of those who were screened (Table 1). At the time of CMR, $\approx 50\%$ of participants had hypertension with the majority (41% of participants) using antihypertensive medications; 11.5% of the participants reported current smoking. Sixty-four percent of the cohort had hypercholesterolemia, with 57% of the cohort treated with lipid-lowering medications.

Compared with the full CMR cohort, participants who had delayed-enhancement CMR had a slightly lower prevalence of hypertension and use of antihypertensive medications, minimally lower mean HbA1c levels ($\approx 0.1\%$ lower), lower total cholesterol (2 mg/dL less), and lower triglyceride levels ($\approx 3$ mg/dL less; Table 1). The Framingham Risk Score$^{24}$ was the same for the entire screened cohort, the CMR cohort, and the gadolinium CMR cohort.

Table 1 also presents the prevalence of diabetic complications at the time of the CMR examination. In participants undergoing CMR, the prevalence of clinical or silent MI was 3.6%, retinopathy was 20.3%, macroalbuminuria or end-stage renal disease was 9.6%, autonomic neuropathy was 31.7%, and peripheral neuropathy was 29.4%. Except for retinopathy, these complication rates were slightly lower than in the participants who screened for CMR.

The CVD characteristics of participants with delayed-enhancement CMR were similar to those of the screened study cohort (Table 1). The prevalences of clinical or silent MI, nonzero coronary artery calcium score, and common carotid artery intima-media thickness were not significantly different among the screened cohort, CMR, and gadolinium CMR participants. However, retinopathy, macroalbuminuria/end-stage renal disease, and autonomic and peripheral neuropathy were less frequent in participants with delayed-enhancement CMR than those without ($P<0.0001$ for all except autonomic neuropathy, $P=0.002$ for autonomic neuropathy).

Table 2 shows measures of cardiovascular function by sex. Except for ejection fraction, ankle-to-arm ratio, and cardiac index, all parameters were higher among men than women. The prevalence of an ankle-to-arm ratio $<0.9$ and ejection fraction were higher in women than in men. Cardiac index was not significantly different between the sexes. Cardiovascular function measures for participants with delayed-enhancement imaging were similar to those of the total cohort with CMR.

**LV Structure and Function in Relation to CVD Risk Factors**

Table 3 presents the multivariate model for LV parameters in relationship to CVD risk factors. LV mass and end-diastolic volume (EDV) were 3.1 g and 4 mL less per each 10-year increase in age and 4 g and 5.1 mL less in the secondary intervention cohort compared with the primary prevention cohort, respectively. LV mass was positively associated
Table 1. Clinical Characteristics of Epidemiology of Diabetes Interventions and Complications Participants at the Time of the Cardiac Magnetic Resonance Examination

<table>
<thead>
<tr>
<th>Demographic Characteristics and Risk Factors</th>
<th>CMR-Screened Participants With Current EDIC Data (n=1240)</th>
<th>Participants With CMR (n=1017)</th>
<th>Participants With Gadolinium CMR (n=741)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49±7</td>
<td>49±7</td>
<td>49±7</td>
</tr>
<tr>
<td>Duration of diabetes mellitus, y</td>
<td>27.6±4.9</td>
<td>27.6±4.9</td>
<td>27.5±4.9</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>12.0</td>
<td>11.5</td>
<td>11.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.4±5.1</td>
<td>28.1±4.7</td>
<td>28.2±4.7</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>26.7±3.7</td>
<td>26.5±3.4</td>
<td>26.5±3.4</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>120±14</td>
<td>120±14</td>
<td>120±14</td>
</tr>
<tr>
<td>Mean SBP, mm Hg</td>
<td>118±8</td>
<td>118±8</td>
<td>118±8</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72±9</td>
<td>72±9</td>
<td>73±9</td>
</tr>
<tr>
<td>Mean DBP, mm Hg</td>
<td>74±5</td>
<td>74±5</td>
<td>74±5</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>51.3</td>
<td>50.3</td>
<td>48.0</td>
</tr>
<tr>
<td>Antihypertensive medication, %</td>
<td>42.3</td>
<td>41.3</td>
<td>39.1</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>173±36</td>
<td>173±36</td>
<td>171±36</td>
</tr>
<tr>
<td>Mean total cholesterol, mg/dL</td>
<td>182±24</td>
<td>182±24</td>
<td>180±23</td>
</tr>
<tr>
<td>Recent HDL, mg/dL</td>
<td>60±18</td>
<td>60±18</td>
<td>59±17</td>
</tr>
<tr>
<td>Mean HDL, mg/dL</td>
<td>55±12</td>
<td>55±13</td>
<td>54±12</td>
</tr>
<tr>
<td>Recent LDL, mg/dL</td>
<td>97±30</td>
<td>97±30</td>
<td>97±30</td>
</tr>
<tr>
<td>Mean LDL, mg/dL</td>
<td>110±21</td>
<td>110±20</td>
<td>110±21</td>
</tr>
<tr>
<td>Recent triglycerides, mg/dL</td>
<td>81±56</td>
<td>80±56</td>
<td>77±52</td>
</tr>
<tr>
<td>Mean triglycerides, mg/dL</td>
<td>85±41</td>
<td>83±40</td>
<td>81±38</td>
</tr>
<tr>
<td>Hypercholesterolemia, %†</td>
<td>63.5</td>
<td>63.7</td>
<td>64.8</td>
</tr>
<tr>
<td>Lipid-lowering medication, %</td>
<td>56.7</td>
<td>57.3</td>
<td>58.2</td>
</tr>
<tr>
<td>Recent HbA1c, %</td>
<td>7.9±1.2</td>
<td>7.9±1.2</td>
<td>7.9±1.2</td>
</tr>
<tr>
<td>Mean HbA1c, %</td>
<td>8.0±1.0</td>
<td>8.0±1.0</td>
<td>7.9±0.9</td>
</tr>
<tr>
<td>Framingham Risk Score</td>
<td>0.06±0.05</td>
<td>0.06±0.04</td>
<td>0.06±0.04</td>
</tr>
<tr>
<td>Diabetes complications, n (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical or silent MI</td>
<td>52 (4.2)</td>
<td>37 (3.6)</td>
<td>28 (3.8)</td>
</tr>
<tr>
<td>Adjudicated clinical MI events</td>
<td>24 (1.9)</td>
<td>14 (1.4)</td>
<td>10 (1.4)</td>
</tr>
<tr>
<td>Silent MI</td>
<td>30 (2.4)</td>
<td>23 (2.3)</td>
<td>18 (2.4)</td>
</tr>
<tr>
<td>CAC score &gt;0 (years 7–9)§</td>
<td>343 (30.6)</td>
<td>282 (30.3)</td>
<td>202 (29.5)</td>
</tr>
<tr>
<td>CAC score &gt;200 (years 7–9)§</td>
<td>88 (7.9)</td>
<td>67 (7.2)</td>
<td>43 (6.3)</td>
</tr>
<tr>
<td>Common IMT (year 12)§</td>
<td>0.69±0.15</td>
<td>0.68±0.14</td>
<td>0.68±0.13</td>
</tr>
<tr>
<td>Retinopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDR or worse</td>
<td>252 (20.3)</td>
<td>206 (20.3)</td>
<td>123 (16.6)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroalbuminuria/ESRD¶</td>
<td>124 (10.0)</td>
<td>98 (9.6)</td>
<td>37 (5.0)</td>
</tr>
<tr>
<td>Sustained microalbuminuria/ESRD#</td>
<td>338 (27.3)</td>
<td>269 (26.5)</td>
<td>157 (21.2)</td>
</tr>
<tr>
<td>Neuropathy**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic neuropathy††</td>
<td>377 (32.2)</td>
<td>310 (31.7)</td>
<td>207 (28.9)</td>
</tr>
<tr>
<td>Peripheral neuropathy‡‡</td>
<td>342 (30.0)</td>
<td>282 (29.4)</td>
<td>178 (25.3)</td>
</tr>
</tbody>
</table>

(Continued)
with smoking, macroalbuminuria, and mean SBP (7.6 g, 8.3 g, and 14.8 g/10 mm Hg, respectively). No significant association was noted between LV mass and mean HbA1c. LV EDV was positively associated with alcohol use (5.6 mL) and inversely associated with mean HbA1c level (−2.9 mL/1%). CVD risk factors accounted for 58% of variability of LV mass and 46% variability of EDV after adjustment for height, weight, and machine type. Stroke volume was 2.2 mL less per each 1% increase in mean HbA1c level, 2.1 mL greater per each 10-mm Hg increase in SBP, and 3.3 mL greater in participants with versus without alcohol use. Neither mean HbA1c nor macroalbuminuria was related to stroke volume.

Ejection fraction was not associated with any traditional risk factors, mean HbA1c, or macroalbuminuria. Cardiac output was directly related to SBP (0.3 L/min per 10 mm Hg) and alcohol use (0.2 L/min) and inversely related to age (−0.3 L/min per 10 years).

Greater ratio of LV mass to EDV indicates concentric remodeling. The ratio of LV mass and EDV is normally close

**Table 1. Imaging Measures of Diabetes Interventions and Complications Participants Among Men and Women in the Full Cardiac Magnetic Resonance Cohort and Among Those With Gadolinium-Delayed Enhancement**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Female (n=486)</th>
<th>Male (n=531)</th>
<th>P*</th>
<th>Female (n=313)</th>
<th>Male (n=428)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass index, g/m²</td>
<td>64.0±10.1</td>
<td>76.6±12.4</td>
<td>&lt;0.0001</td>
<td>63.9±9.2</td>
<td>75.7±11.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>End-diastolic volume index, mL/m²</td>
<td>65.8±9.7</td>
<td>73.3±12.6</td>
<td>&lt;0.0001</td>
<td>66.4±9.3</td>
<td>73.7±12.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>End-systolic volume index, mL/m²</td>
<td>24.6±6.4</td>
<td>29.3±7.8</td>
<td>&lt;0.0001</td>
<td>25.2±6.0</td>
<td>29.6±7.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td>41.3±6.4</td>
<td>44.0±8.1</td>
<td>&lt;0.0001</td>
<td>41.2±6.1</td>
<td>44.1±8.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac index, L·min⁻¹·m⁻²</td>
<td>2.97±0.56</td>
<td>3.05±0.62</td>
<td>0.1116</td>
<td>2.99±0.52</td>
<td>3.04±0.62</td>
<td>0.5419</td>
</tr>
<tr>
<td>LV mass/volume ratio, mg/mL</td>
<td>0.98±0.15</td>
<td>1.06±0.18</td>
<td>&lt;0.0001</td>
<td>0.97±0.14</td>
<td>1.04±0.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>62.9±6.2</td>
<td>60.3±6.3</td>
<td>&lt;0.0001</td>
<td>62.2±5.8</td>
<td>60.0±6.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAC score &gt;0 (year 7–9), %†</td>
<td>20.6</td>
<td>38.7</td>
<td>&lt;0.0001</td>
<td>19.6</td>
<td>36.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CAC score &gt;200 (year 7–9), %‡</td>
<td>3.9</td>
<td>10.1</td>
<td>0.0003</td>
<td>3.9</td>
<td>7.9</td>
<td>0.0328</td>
</tr>
<tr>
<td>Common IMT (year 12)‡</td>
<td>0.65±0.10</td>
<td>0.71±0.16</td>
<td>&lt;0.0001</td>
<td>0.65±0.10</td>
<td>0.70±0.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ankle/arm ratio &lt;0.9, %</td>
<td>16.7</td>
<td>9.6</td>
<td>0.0008</td>
<td>15.0</td>
<td>7.9</td>
<td>0.0023</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; CAC, coronary artery calcium; and IMT, intima-media thickness.

*P for men versus women is based on the x² test for categorical variables and Wilcoxon rank-sum test for continuous variables.
†n=932 and 684 for CMR participants and DE participants, respectively.
‡n=889 and 650 for CMR participants and DE participants, respectively.
to unity for both men and women. The ratio of LV mass to EDV showed a positive relationship to SBP (0.05 g/mL per 10 mm Hg, mean HbA1C (0.03 mL/1%), and macroalbuminuria (0.08 g/mL with positive history of macroalbuminuria). There was no relationship of study cohort to cardiac output and ratio of LV mass to EDV.

Owing to the correlation between height and weight, additional analyses like those in Table 3 were conducted without adjustment for height and weight or for appropriate measures using values indexed to (divided by) body surface area (see the Results section and Table IIA and IIB in the online-only Data Supplement). The direction and magnitude of significant associations in Table 3 were similar after these analyses.

Additional models were also explored in which a value of 10 mm Hg was added to all SBP values obtained while a subject was taking antihypertensive medications before calculating the weighted mean for each subject. Stroke volume was no longer significant with this approach (estimate, 1.9 mL [SE, 0.6 mL] per 10 mm Hg increment in SBP compared with values of 2.1 mL [SE, 0.6 mL] per 10 mm Hg increment in SBP shown in Table 3). LV mass, cardiac output, and LV mass/EDV showed no substantial effect of this SBP adjustment.

### Prevalence of Myocardial Scar

The overall prevalence of myocardial scar was 4.3% (32 of 741). Sixteen patients had ischemic scar (Figure 2A) and 16 had nonischemic scar (Figure 2B). Men had a higher prevalence of scar compared with women (5.8% versus 2.2%, respectively; P<0.05). The average mass of ischemic scar was 3.3±4.5 g (P<0.05).

Among the 32 participants with myocardial scar by CMR imaging, only 6 (19%) had previously experienced a clinically adjudicated MI; all 6 of these participants had an ischemic myocardial scar by CMR (Table 4). Five of 32 participants (16%) had evidence of silent MI. Among these 5 participants, 3 had ischemic and 2 had nonischemic myocardial scarring. Of those without a myocardial scar by CMR (n=709), 4 (0.6%) had an adjudicated clinical MI and 13 (1.8%) had an ECG-defined silent MI (Table 4). Of EDIC participants with no evidence of adjudicated MI or ECG-defined MI (n=713), 21 (2.9%) had CMR-defined scars, most of which were an nonischemic rather than ischemic pattern (14 of 21, 66.7%; Table 4).

### Myocardial Scar in Relation to CVD Risk Factors

Table 5 presents separate, minimally adjusted logistic regression models to assess the influence of individual factors on the prevalence of myocardial scar.
the risk of myocardial scar. With only 32 subjects with observed scars, the data were insufficient to permit a more robust multivariate analysis.

Male patients had 2.5 (95% CI, 1.1–5.9) times higher odds (risk) of having myocardial scar compared with female patients (P=0.034; Table 5). Each 10-year increase in age was associated with a 2.2-fold (95% CI, 1.2–4.0) higher risk of myocardial scar (P=0.008). Hypertensive participants (including those on antihypertensive medications) had 2.4-fold (95% CI, 1.1–5.2) higher odds of having myocardial scar than normotensive participants. Participants who had higher mean high-density lipoprotein cholesterol had a lower risk of having myocardial scar (odds ratio, 0.96 [95% CI, 0.93–1.00] per 1-mg/dL higher mean high-density lipoprotein cholesterol; P=0.043). Participants with higher mean HbA1c had 1.5-fold greater odds of having myocardial scar per 1% increase (P=0.049). Additionally, participants with macroalbuminuria also had 4.0-fold (95% CI, 1.4–11.6) higher odds of having myocardial scar compared with those without macroalbuminuria (P=0.011; Table 5).

Greater LV mass, end-systolic volume, and EDV indexes were significantly associated with higher odds for myocardial scar (adjusted odds ratios, 1.04 [95% CI, 1.0–1.1] per 1-g/m² increase in LV mass index, P=0.022; 1.03 [95% CI, 1.0–1.1] per 1-mL/m² increase in EDV index, P=0.016; 1.10 [95% CI, 1.05–1.14] per 1-mL/m² increase in end-systolic volume index, P<0.0001; Table 5). The odds of myocardial scar was greater in association with lower ejection fraction (adjusted odds ratio, 0.86; [95% CI, 0.8–0.9] per 1% increase in ejection fraction; P<0.0001; Table 5).

### Discussion

The DCCT/EDIC is the first large-scale cohort of patients with type 1 diabetes mellitus evaluated by CMR. The main conclusions are the following: (1) Mean SBP, smoking, and macroalbuminuria were associated with greater LV mass, with the magnitude of the associations greatest for patients with macroalbuminuria; (2) higher mean HbA1c (over ≈22 years of follow-up) was associated with smaller LV volumes but similar LV mass when adjusted for other risk factors; (3) ratio of LV mass to volume, an indicator of concentric LV remodeling, was positively associated with mean SBP, macroalbuminuria, and mean HbA1c, and (4) the prevalence of myocardial scar by CMR was 4.3% compared with only 1.4% of patients with clinically recognized MI. Older age, male sex, hypertension, macroalbuminuria, elevated mean HbA1c, reduced high-density lipoprotein levels, greater LV mass and volume index, and reduced global LV function were associated with a higher risk of myocardial scar.

The term diabetic cardiomyopathy refers to diabetic patients with LV dysfunction with signs and symptoms of heart failure. Stage 1 diabetic cardiomyopathy, the earliest form, has been characterized by diastolic dysfunction with normal global ejection fraction. Adverse myocardial remodeling, defined by a greater ratio of LV mass to EDV, and LV hypertrophy contribute to diastolic dysfunction and are independent predictors of cardiovascular events in the general population.

Greater LV mass was observed in type 1 diabetes mellitus when the disease was complicated with nephropathy or autonomic neuropathy but not in uncomplicated diabetes mellitus. Whether LV hypertrophy is independent of modifiable risk factor in type 2 diabetes mellitus is controversial. Our findings extend previous studies by showing macroalbuminuria as the strongest determinant of LV mass among the markers assessed in type 1 diabetes mellitus.

Greater LV mass was also
CMR-identified myocardial scar, an important predictor of adverse cardiovascular outcomes, was present in 28% of symptomatic type 2 diabetics (107 patients; mean age, 63 years), 24% of elderly subjects at 70 years of age (248 subjects), and 9.4% of patients with manifest arterial disease or marked risk factors for atherosclerosis (480 patients; mean age, 53 years). The DCCT/EDIC cohort has a low rate of myocardial scar (4.3%), albeit in younger patients who were mostly asymptomatic. Reduced global LV function and greater LV mass were associated with the presence of myocardial scar in prior reports, similar to our results in the DCCT/EDIC cohort. These results suggest that determinants of myocardial scar may be similar across a wide range of subjects who have a high risk profile for CVD. Additionally, DCCT/EDIC participants with hypertension, macroalbuminuria, and higher mean HbA1c and those using lipid-lowering medications had higher odds of having myocardial scar.

The concordance between history of MI and the presence of myocardial scar was relatively low. Approximately 65% of participants who had myocardial scar by CMR had no clinical evidence of prior MI. Similar to our findings, Kwong et al (195 patients) and Kim et al (85 patients) reported that most patients with myocardial scar by CMR did not have significant Q-wave changes. “Pathological” Q waves are not 100% specific and may underestimate or overestimate the true prevalence of silent MI. Conversely, in our cohort, CMR-defined myocardial scar was not present in 4 patients with adjudicated MI. Reasons for this discrepancy could include very small scar size, successful revascularization of coronary stenosis before scar tissue develops, incorrect adjudication, or interval resolution of myocardial scar.

There are several limitations of the present study. Of the 1240 subjects who were screened in EDIC, ~18% (n = 223) did not complete the CMR examination. Of 1017 participants with CMR, 262 (26%) were excluded from gadolinium administration mainly as a result of moderate or worse renal dysfunction, renal transplantation, or dialysis. The risk for myocardial scar in the excluded participants may be higher than in those patients who were included. Coronary angiograms were not available; thus, we do not know whether CMR scar in our cohort is due to microvascular complications of diabetes mellitus or to occlusive coronary artery disease. In addition, nonischemic CMR scar can be seen in a wide range of nondiabetic, nonischemic cardiomyopathies such as myocarditis and hypertrophic and dilated cardiomyopathy.

The DCCT/EDIC cohort may not be representative of patients with type 1 diabetes mellitus in the community owing to long-term cohort evaluation. There was no significant difference in incidence of clinical or silent MI between 741 participants and 276 nonparticipants in the gadolinium CMR. However, patients with a potentially healthier cardiovascular profile underwent CMR. Interestingly, despite the exclusion of patients with moderate or severe renal insufficiency, the presence of macroalbuminuria was associated with a 3.5-fold higher likelihood of myocardial scar.
Conclusions
LV mass was positively associated with smoking and SBP and most strongly associated with macroalbuminuria but not with HbA1c. The prevalence of myocardial scar in the DCCT/EDIC type 1 diabetic cohort was 4.3%. In addition to traditional risk factors, higher mean HbA1c and macroalbuminuria were strongly associated with myocardial scar in patients with type 1 diabetes mellitus, supporting the potential clinical importance of these scars. Further follow-up is necessary to clarify the clinical significance of myocardial scars in type 1 diabetes mellitus.

Acknowledgments
A complete list of the members of the DCCT/EDIC Research Group can be found in Archives of Ophthalmology (2008;126:1713). The participating radiologists and technologists are listed in the online Data Supplement. Contributors of free or discounted supplies and/or equipment were Lifescan, Roche, Aventis, Eli Lilly, Omni-Pod, Can-Am, B-D, Animas, Medtronic, Medtronic Minimed, Bayer (donation 1 time in 2008), and Omron. We acknowledge the data processing and technical assistance of Wanyu Hsu at the Biostatistics Center at George Washington University.

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Disclosures
Dr van der Geest is a consultant for Medis medical imaging systems. The other authors report no conflicts.

References
CLINICAL PERSPECTIVE

Type 1 diabetes mellitus is associated with a relatively high prevalence of cardiovascular disease and clinical and silent myocardial infarction compared with the nondiabetic population, leading to alterations in cardiac structure and function. In the present study, we evaluated the relationship of cardiovascular disease risk factors, including hemoglobin A1c levels and diabetic nephropathy, to myocardial structure, function, and scar by cardiac magnetic resonance imaging in 1017 patients of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. The DCCT/EDIC study is the first large-scale cohort of patients with type 1 diabetes mellitus. Patients had a mean clinical evaluation period of 22 years preceding cardiac magnetic resonance. We found that macroalbuminuria and mean hemoglobin A1c (over 22 years of follow-up) were significant risk factors for alterations in left ventricular structure and function and for having myocardial scar. The prevalence of myocardial scar by cardiac magnetic resonance was 4.3% compared with only 1.4% in patients with clinically recognized myocardial infarction. The concordance of scar and clinical history was relatively low. These findings suggest that modifiable cardiovascular disease risk factors and glycemic control play a significant role in relationship to cardiovascular morbidity and mortality in patients with type 1 diabetes mellitus.
Myocardial Structure, Function, and Scar in Patients With Type 1 Diabetes Mellitus

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SUPPLEMENTAL MATERIAL

Supplemental Material: List of the participating radiologists and technologists

Radiologists

Technologists
Supplemental Methods: Image Analysis

CMR examinations consisted of cine images for LV function and delayed gadolinium images for myocardial scar. Cine CMR was acquired with temporal resolution 30-50 msec in two-chamber, four-chamber and short axis planes using a steady-state free-precession (SSFP) pulse sequence. To detect myocardial scar, a spoiled gradient recalled echo (GRE) pulse was used with phase sensitive inversion recovery (when available) in short axis, two and four chamber planes beginning 15 minutes after intravenous administration of 0.15-0.20 mmol/kg dose of gadolinium-based contrast. Inversion times were individually adjusted to null the signal from normal myocardium.

All CMR studies were evaluated and quantified centrally at Johns Hopkins University Hospital, Baltimore, MD by readers who were blinded to the subjects’ clinical information. Left ventricular (LV) mass, volumes and functional parameters were determined from short axis cine images covering the heart from base to apex throughout the cardiac cycle using QMASS software (version 6, Medis, Leiden, the Netherlands). Left ventricular endocardial and epicardial contours were traced manually at both end-diastole and end-systole by one physician reader and checked by a second CMR physician with 15 years experience. Papillary muscles were included in the LV end-diastolic volume (EDV) determinations and LV end-systolic volume (ESV), and excluded from LV mass measurements. LV EDV and LV ESV were calculated using Simpson’s rule (the summation of areas on each separate slice multiplied by the sum of slice thickness and image gap). LV mass was determined using the sum of the myocardial area (the difference between endocardial and epicardial contour) multiplied by slice thickness plus image gap in the end-diastolic phase multiplied by the specific gravity of myocardium (1.05 g/ml). LV stroke volume (SV) was calculated as the difference between LV EDV and LV ESV. LV ejection fraction (EF) was calculated using LV SV divided by LVEDV and multiplied by 100 (percent). Cardiac output was calculated as LV SV times the heart rate. LV mass and volumes were indexed to body surface area $[\text{BSA (m}^2) = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}]$ when appropriate.
Supplemental Table 1: CMR intra-class correlation and %TEM (95% confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>Correlation (95% confidence interval)</th>
<th>%TEM - Percentage reading variability relative to the mean (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of re-reads</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>LV end diastolic volume</td>
<td>0.978 (0.968 – 0.985)</td>
<td>3.19 (2.64 – 3.74)</td>
</tr>
<tr>
<td>LV end systolic volume</td>
<td>0.964 (0.948 – 0.976)</td>
<td>5.08 (4.31 – 5.90)</td>
</tr>
<tr>
<td>LV stroke volume index</td>
<td>0.968 (0.952 – 0.978)</td>
<td>4.37 (3.52 – 5.24)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>0.917 (0.879 – 0.943)</td>
<td>2.89 (2.40 – 3.39)</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>0.963 (0.946 – 0.975)</td>
<td>4.26 (3.49 – 5.05)</td>
</tr>
<tr>
<td>LV mass</td>
<td>0.958 (0.938 – 0.972)</td>
<td>4.52 (3.79 – 5.28)</td>
</tr>
</tbody>
</table>
Supplemental Results: Additional Multivariable Analysis of Traditional Cardiovascular (CV) Risk Factors in Relation to LV Structure and Function (including macroalbuminuria).

It is generally accepted that it is necessary to adjust for body size when evaluating measures of cardiac size and function as recently reviewed \(^1,^2\). A number of the papers describing the use of such measures in epidemiological analyses have employed indexed values, such as LVMass/BSA (body surface area). The majority of indices have been developed for echocardiography or MRI using fast gradient echo imaging. Rather than use indexed values herein, we adjusted for both height and weight because such indices have not yet been validated patients with type 1 diabetes evaluated by cardiac MRI, and because a covariate adjustment will effectively compensate for the dependence of the cardiac measures on body size.

However, inclusion of highly correlated covariates in a model can lead to biased or invalid results, statistically termed multicollinearity. The correlation between height and weight in these analyses is 0.57. To assess whether multicollinearity affected the results herein, additional analyses were conducted of the associations as shown in Table 3 of the paper, either not adjusting for height and weight, or by indexing all variables (other than ejection fraction) for body surface area.

Table 2A presents the results of the analyses without adjustment for height and weight. To facilitate comparison to Table 3 of the paper, effects are only flagged (*) to denote statistical significance at the 0.05 level both before and after adjustment for multiple tests. Of the 25 instances in which a covariate was significantly associated with a cMRI measure, 24 were also significant without adjustment for height and weight (the association between smoking and LV mass). However, 5 additional associations became significant in Table 2A (SBP with end diastolic and systolic volumes; gender with stroke volume, and gender and cohort with cardiac output).

Table 2B presents an additional analysis of appropriate CMR measures indexed to body surface area (not including ejection fraction and the LV mass to EDV ratio), again without the adjustment for height and weight. All significant associations in Table 3 of the paper for these measures were also significant in Table 2B and one additional association became significant (gender with stroke volume).
Thus, adjustment for height and weight in Table 3 of the paper, if anything was slightly conservative relative to analyses without such adjustment or using indexed values.

References

Supplemental Table 2A: Multivariable analysis of traditional cardiovascular (CV) risk factors in relation to LV structure and function (including macroalbuminuria). No adjustment for weight and height.

<table>
<thead>
<tr>
<th>Proportion of variability explained by full model†</th>
<th>LV Mass (g)</th>
<th>End Diastolic Volume (ml)</th>
<th>End Systolic Volume (ml)</th>
<th>Stroke Volume (ml)</th>
<th>Ejection Fraction (%)</th>
<th>Cardiac Output (L/min)</th>
<th>LV Mass/EDV (g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53.9%</td>
<td>34.8%</td>
<td>25.0%</td>
<td>27.8%</td>
<td>6.6%</td>
<td>22.0%</td>
<td>19.6%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factor, estimate (standard error)</th>
<th>Age (per 10 years)</th>
<th>Gender (women vs. men)</th>
<th>Cohort (2° vs. 1°)</th>
<th>Smoking (yes vs. no)</th>
<th>Alcohol use (yes vs. no)</th>
<th>Mean SBP (per 10 mm Hg)</th>
<th>Mean HDL (mg/dl)</th>
<th>Mean LDL (mg/dl)</th>
<th>Mean HbA1C (%)</th>
<th>History of AER ≥ 300 (yes vs. no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3.0 (1.1)*</td>
<td>-3.5 (1.2)*</td>
<td>-14.9 (1.1)$^\dagger$</td>
<td>-5.8 (1.4)*</td>
<td>5.3 (2.2)</td>
<td>3.5 (1.5)</td>
<td>11.6 (1.0)*</td>
<td>-0.1 (0.07)</td>
<td>-0.05 (0.04)</td>
<td>-0.3 (0.8)</td>
<td>10.7 (2.7)*</td>
</tr>
<tr>
<td>-3.5 (1.2)*</td>
<td>-28.9 (1.8)$^*$</td>
<td>-14.0 (1.2)$^*$</td>
<td>-7.1 (1.6)*</td>
<td>-0.1 (2.5)</td>
<td>5.9 (1.6)$^*$</td>
<td>6.1 (1.1)$^*$</td>
<td>-0.03 (0.07)</td>
<td>-0.07 (0.04)</td>
<td>2.6 (0.9)$^*$</td>
<td>-1.8 (2.9)</td>
</tr>
<tr>
<td>-2.1 (0.7)$^*$</td>
<td>-1.5 (0.8)</td>
<td>2.9 (0.5)$^*$</td>
<td>-2.0 (1.0)</td>
<td>0.9 (1.5)</td>
<td>2.5 (1.0)</td>
<td>1.9 (0.6)$^*$</td>
<td>-0.02 (0.04)</td>
<td>-0.03 (0.02)</td>
<td>-0.5 (0.5)</td>
<td>-1.7 (2.9)$^*$</td>
</tr>
<tr>
<td>-1.5 (0.8)</td>
<td>-5.1 (1.0)$^*$</td>
<td>-0.6 (0.4)</td>
<td>-1.1 (1.6)</td>
<td>-1.1 (1.6)</td>
<td>3.4 (1.0)$^*$</td>
<td>4.2 (0.7)$^*$</td>
<td>-0.01 (0.04)</td>
<td>-0.05 (0.03)</td>
<td>-0.2 (0.6)$^*$</td>
<td>-1.7 (1.8)$^*$</td>
</tr>
<tr>
<td>0.6 (0.3)</td>
<td>-0.6 (0.4)</td>
<td>0.09 (0.1)</td>
<td>-0.5 (0.6)</td>
<td>0.0 (0.6)</td>
<td>0.3 (0.4)</td>
<td>0.5 (0.3)</td>
<td>0.008 (0.02)</td>
<td>-0.003 (0.01)</td>
<td>0.4 (0.2)</td>
<td>0.1 (1.9)</td>
</tr>
<tr>
<td>-0.3 (0.06)$^*$</td>
<td>-0.2 (0.08)$^*$</td>
<td>0.09 (0.1)</td>
<td>0.008 (0.02)</td>
<td>0.008 (0.02)</td>
<td>0.2 (0.08)$^*$</td>
<td>0.4 (0.05)$^*$</td>
<td>-0.002 (0.004)</td>
<td>0.001 (0.002)</td>
<td>0.07 (0.04)</td>
<td>0.0 (7.6)</td>
</tr>
<tr>
<td>0.006 (0.008)</td>
<td>-0.04 (0.01)$^*$</td>
<td>0.01 (0.01)</td>
<td>0.01 (0.01)</td>
<td>0.04 (0.02)</td>
<td>0.01 (0.01)</td>
<td>0.04 (0.007)$^*$</td>
<td>-0.001 (0.0004)</td>
<td>0.0002 (0.0002)</td>
<td>0.02 (0.06)$^*$</td>
<td>0.0 (8.2)$^*$</td>
</tr>
</tbody>
</table>

† In addition to the above factors, the full model includes the machine type.

Cohort (2° vs. 1°): secondary intervention cohort that had diabetes for 1-15 years with mild to moderate non-proliferative retinopathy and urinary albumin excretion rate < 200 mg/dl in the DCCT versus primary prevention cohort had diabetes for 1-5 years with no related complications.

SBP: systolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein

AER: albumin excretion rate

* p ≤ 0.05 after Hochberg corrections for multiple tests.
Supplemental Table 2B: Multivariable analysis of traditional cardiovascular (CV) risk factors in relation to LV structure and function (including macroalbuminuria) for Measures Indexed to Body Surface Area (BSA), with no adjustment for weight and height.

<table>
<thead>
<tr>
<th>Risk factor, estimate (standard error)</th>
<th>LV Mass/BSA (g/m)</th>
<th>End Diastolic Volume/BSA (ml/m)</th>
<th>End Systolic Volume/BSA (ml/m)</th>
<th>Stroke Volume/BSA (ml/m)</th>
<th>Cardiac Output/BSA (L/min/m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of variability explained by full model†</td>
<td>37.4%</td>
<td>16.9%</td>
<td>12.8%</td>
<td>11.6%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>-1.5 (0.5) †</td>
<td>-1.7 (0.5) *</td>
<td>-1.0 (0.4) *</td>
<td>-0.7 (0.4)</td>
<td>-0.2 (0.03) *</td>
</tr>
<tr>
<td>Gender (women vs. men)</td>
<td>-10.1 (0.8) *</td>
<td>-7.2 (0.8) *</td>
<td>-4.7 (0.5) *</td>
<td>-2.5 (0.5) *</td>
<td>-0.03 (0.04)</td>
</tr>
<tr>
<td>Cohort (2° vs. 1°)</td>
<td>-1.8 (0.7) *</td>
<td>-2.5 (0.7) *</td>
<td>-0.6 (0.5)</td>
<td>-1.9 (0.5) *</td>
<td>-0.08 (0.04)</td>
</tr>
<tr>
<td>Smoking (yes vs. no)</td>
<td>4.4 (1.0) *</td>
<td>1.5 (1.1)</td>
<td>1.1 (0.7)</td>
<td>0.4 (0.7)</td>
<td>0.1 (0.06)</td>
</tr>
<tr>
<td>Alcohol use (yes vs. no)</td>
<td>1.7 (0.7)</td>
<td>2.7 (0.7) *</td>
<td>1.2 (0.5)</td>
<td>1.6 (0.5) *</td>
<td>0.1 (0.03) *</td>
</tr>
<tr>
<td>Mean SBP (per 10 mm Hg)</td>
<td>3.8 (0.4) *</td>
<td>1.1 (0.5)</td>
<td>0.2 (0.3)</td>
<td>0.9 (0.3) *</td>
<td>0.1 (0.02) *</td>
</tr>
<tr>
<td>Mean HDL (mg/dl)</td>
<td>0.01 (0.03)</td>
<td>0.07 (0.03)</td>
<td>0.02 (0.02)</td>
<td>0.05 (0.02)</td>
<td>0.003 (0.002)</td>
</tr>
<tr>
<td>Mean LDL (mg/dl)</td>
<td>-0.04 (0.02)</td>
<td>-0.05 (0.02)</td>
<td>-0.02 (0.01)</td>
<td>-0.03 (0.01)</td>
<td>-0.001 (0.0009)</td>
</tr>
<tr>
<td>Mean HbA1C (%)</td>
<td>-0.2 (0.4)</td>
<td>-1.5 (0.4) *</td>
<td>-0.3 (0.3)</td>
<td>-1.2 (0.3) *</td>
<td>0.03 (0.02)</td>
</tr>
<tr>
<td>History of AER ≥ 300 (yes vs. no)</td>
<td>7.7 (1.2) *</td>
<td>1.3 (1.3)</td>
<td>-0.06 (0.8)</td>
<td>1.3 (0.8)</td>
<td>0.1 (0.06)</td>
</tr>
</tbody>
</table>

† In addition to the above factors, the full model includes the machine type.

Cohort (2° vs. 1°): secondary intervention cohort that had diabetes for 1-15 years with mild to moderate non-proliferative retinopathy and urinary albumin excretion rate < 200 mg/dl in the DCCT versus primary prevention cohort had diabetes for 1-5 years with no related complications.

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