Glycemic Control and Cardiovascular Events in Diabetic Hemodialysis Patients

Christiane Drechsler, MD, MSc; Vera Krane, MD; Eberhard Ritz, MD; Winfried März, MD; Christoph Wanner, MD

Background—Patients on maintenance dialysis treatment experience an excess mortality, predominantly of sudden cardiac death. Poor glycemic control is associated with cardiovascular comorbidities in the general population. This study investigated the impact of glycemic control on cardiac and vascular outcomes in diabetic hemodialysis patients.

Methods and Results—Glycohemoglobin A1c (HbA1c) was measured in 1255 hemodialysis patients with type 2 diabetes mellitus who participated in the German Diabetes and Dialysis Study (4D Study) and were followed up for a median of 4 years. Using Cox regression analyses, we determined hazard ratios to reach prespecified, adjudicated end points according to HbA1c levels at baseline: sudden cardiac death (n=160), myocardial infarction (n=200), stroke (n=103), cardiovascular events (n=469), death caused by heart failure (n=41), and all-cause mortality (n=617). Patients had a mean age of 66±8 years (54% male) and mean HbA1c of 6.7±1.3%. Patients with an HbA1c >8% had a 2-fold higher risk of sudden death compared with those with an HbA1c ≤6% (hazard ratio, 2.14; 95% confidence interval, 1.33 to 3.44), persisting in multivariate models. With each 1% increase in HbA1c, the risk of sudden death rose significantly by 18%; similarly, cardiovascular events and mortality increased by 8%. There was a trend for higher risks of stroke and deaths resulting from heart failure, whereas myocardial infarction was not affected. The increased risks of both cardiovascular events and mortality were explained mainly by the impact of HbA1c on sudden death.

Conclusions—Poor glycemic control was strongly associated with sudden cardiac death in diabetic hemodialysis patients, which accounted for increased cardiovascular events and mortality. In contrast, myocardial infarction was not affected. Whether interventions achieving tight glycemic control decrease sudden death requires further evaluation.


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Key Words: cardiovascular diseases ■ death, sudden ■ diabetes mellitus ■ epidemiology ■ kidney

The rate of death of dialysis patients is abysmal. The European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) registry reports an 18% first-year mortality rate,1 whereas the US Renal Data System reports an even higher annual mortality rate of 20%.2 At 41%, cardiac disease is the leading cause of death among dialysis patients.2 The major event is sudden cardiac death, which as a single cause accounts for 26% to 27% of all deaths in dialysis patients.2,3 It is important to identify risk factors for sudden cardiac death in relation to other cardiac and vascular events to develop interventional strategies and to reduce the excess mortality of these patients.

Clinical Perspective on p 2428

Diabetes mellitus is a growing health problem and a risk factor for the development and progression of chronic kidney disease. Almost one half of the US dialysis patients developed end-stage renal disease as a result of type 2 diabetes mellitus (T2DM).2 These patients have a higher comorbidity and poorer outcome compared with nondiabetic patients on dialysis,2 as reflected by a 5-year survival of only 35%.4

Poor glycemic control is associated with the development of comorbidities such as coronary artery disease and myocardial infarction (MI) in the general population.5,6 It has been shown that these are predisposing conditions for sudden cardiac death.7 Furthermore, glycemia is known to influence the electrolyte balance, the function of potassium and calcium channels, and sympathetic activity, all relevant in the arrhythmogenesis of patients with kidney failure.8–10 We therefore hypothesized that glycemic state is a risk factor for sudden cardiac death in dialysis patients.

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The original German Diabetes and Dialysis Study (4D) study was designed in 1997 when regulations did not yet include registration. Therefore, the study does not have a unique identifier at www.clinicaltrials.gov; it is, however, included in www.clinicalstudyresults.org.

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To that end, we investigated the association of hemoglobin A1c (HbA_{1c}) with the risk of sudden cardiac death, MI, stroke, combined cardiovascular events (CVE), death resulting from heart failure, and all-cause mortality in hemodialysis patients. We analyzed data from the German Diabetes Dialysis Study (Die Deutsche Diabetes Dialyse Studie [4D Study]), which evaluated atorvastatin in 1255 patients with T2DM on maintenance hemodialysis.^{3}

**Methods**

**Study Design and Participants**

The 4D study methodology has previously been reported in detail.^{11} Briefly, the 4D study was a prospective randomized controlled trial including 1255 patients with T2DM who were 18 to 80 years of age and had been on hemodialysis for <2 years. Between March 1998 and October 2002, patients were recruited in 178 dialysis centers in Germany. After a period of 4 weeks, patients were randomly assigned to double-blind treatment with either 20 mg atorvastatin (n = 619) or placebo (n = 636) once daily. Study visits took place 3 times before randomization (visits 1 through 3), at randomization (visit 4), at 4 weeks (visit 5), and at every 6 months (visit 6, etc) after randomization until the date of death, censoring, or end of the study in March 2004. The primary end point of the 4D Study was defined as a composite of death resulting from cardiac causes, fatal or nonfatal stroke, and nonfatal MI, whichever occurred first (composite cardiovascular end point was CVE). Death resulting from cardiac causes comprised sudden death, fatal MI, death caused by congestive heart failure, death resulting from coronary heart disease during or within 28 days after an intervention, and all other deaths ascribed to coronary heart disease. Sudden death was considered death as verified by terminal rhythm disorders in an ECG, witness-observed death within 1 hour after the onset of cardiac symptoms, death confirmed by autopsy, and unexpected death presumably or possibly of cardiac origin and in the absence of a potassium level \( \geq \) 7.5 mmol/L before the start of the 3 most recent sessions of hemodialysis. MI was diagnosed when 2 of the following 3 criteria were met: typical symptoms, elevated levels of cardiac enzymes (ie, a level of creatine kinase-MB >5% of the total level of creatine kinase, a level of lactic dehydrogenase 1.5 times the upper limit of normal, or a level of troponin T >2 ng/mL), or diagnostic changes on the ECG. When death occurred within 28 days after an MI as diagnosed above, it was specified as death caused by MI. The classifications were made exclusively with fatal MI being classified only as MI death. Nonfatal MI were classified as other MI. 4D Study end points were centrally adjudicated by 3 members of the end point committee blinded to study treatment and according to predefined criteria.

For the present analysis, sudden cardiac death, MI (fatal and nonfatal), stroke (fatal and nonfatal), the primary end point (CVE), death resulting from congestive heart failure, and all-cause mortality were all chosen to be separate outcome measures and were based on the primary judgment of the end point committee during the 4D Study. The study was approved by the medical ethics committee, and all patients gave their written informed consent before inclusion.

**Data Collection**

Information on age, sex, and smoking status was obtained through patient interviews. Smoking status was classified as never, former, or current. Comorbidities, including the presence of coronary artery disease and congestive heart failure, as well as the duration of diabetes mellitus and dialysis treatment were reported by the patients' nephrologists. Coronary artery disease was defined by history of MI, coronary artery bypass grafting surgery, percutaneous coronary intervention, and the presence of coronary heart disease as documented by coronary angiography. Blood pressure was measured in subjects in the sitting position. Body mass index was calculated as weight (kg) divided by height (m) squared. All laboratory measurements of the 4D Study were performed centrally at the Department of Clinical Chemistry, University of Freiburg, Freiburg, Germany. HbA_{1c} was measured in blood samples taken at baseline at study visit 3 (1 week before randomization) with high-performance liquid chromatography.^{12} Interassay coefficients of variance were <5%. All blood samples were taken before the start of dialysis sessions and administration of drugs.

**Statistical Analysis**

Continuous variables are expressed as mean with SD or median with interquartile range as appropriate. Categorical variables are expressed as percentages.

The study population was divided into 3 groups according to HbA_{1c} levels at baseline: normal, \( \leq \) 6%; elevated, >6% to \( \leq \) 8%; and high, >8%. First, we assessed the association of baseline HbA_{1c} with sudden death as both a continuous and a categorical variable. For the latter, the patients with an HbA_{1c} \( \leq \) 6% were used as the reference group. Absolute (incidence) rates were calculated as the number of events occurring per 100 person-years of follow-up. Kaplan–Meier curves were performed in each HbA_{1c} group, and the log-rank test was computed to compare curves. By Cox regression analyses, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated. The Cox regression analyses were adjusted for the confounders age; sex; atorvastatin treatment; systolic blood pressure; duration of T2DM; time on dialysis; smoking status; body mass index; levels of low-density lipoprotein cholesterol, triglycerides, albumin, hemoglobin, calcium, phosphate, and C-reactive protein; and the presence of coronary artery disease and congestive heart failure (main model). Second, we performed additional Cox regression analyses including potassium and ECG variables, which may represent intermediate conditions lying in the causal pathway of the effect of glycemic control on sudden death. The variables were included 1 at a time to see the magnitude by which the effect estimate for the risk of HbA_{1c} on sudden death changed. Furthermore, in an analysis aiming to assess the impact of all intermediate variables together, they were added simultaneously to the main model. Third, we investigated HbA_{1c} and the risk of other adverse cardiac and vascular outcomes, including MI, stroke, the combined primary end point (CVE), and death resulting from heart failure, to distinguish whether the potential effects of glycemic control are specific for sudden death or generally influence cardiac and vascular outcomes. To see whether a potential impact on the primary end point is explained mainly through the effect of HbA_{1c} on sudden death, we also assessed the risks of HbA_{1c} on CVE except for sudden death. Fourth, we similarly determined the association of HbA_{1c} with all-cause mortality and assessed the risks of HbA_{1c} on all deaths except sudden death. Finally, to test the robustness of our results, we divided the study population into quartiles of HbA_{1c} at baseline and repeated our analyses on the effect of glycemic control on all outcomes using this alternative categorization of HbA_{1c}. We furthermore repeated all analyses in the placebo group only to eliminate any potential influence by atorvastatin treatment. All P values reported are 2 sided. Analyses were performed with SPSS version 16.0 (SPSS Inc, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Patient Characteristics**

Between March 1998 and October 2002, a total of 1255 patients were included into the 4D Study and had an HbA_{1c} measurement at baseline. The mean follow-up period was 3.96 years (median, 4.0 years) on atorvastatin and 3.91 years (median, 4.08 years) on placebo. During follow-up, 469 patients reached the primary end point of CVE. A total of 617 patients died; of those, 160 patients had sudden cardiac death. Another 41 patients died of congestive heart failure, 200 patients experienced an MI (fatal or nonfatal), and 103 patients experienced a stroke (fatal or nonfatal).
In the study population (n=1255), the mean age was 65.7 years (SD, 8.3 years), and 54% of the patients were male. The mean baseline HbA1c level was 6.7% (SD, 1.3%), with no significant difference between the atorvastatin and placebo groups. The baseline patient characteristics are shown in Table 1.

### Baseline HbA1c and Risk of Sudden Death

The absolute rates of sudden cardiac death were high and increased over the categories of HbA1c: 3.0 per 100 person-years in the group with an HbA1c ≤6%, 5.0 per 100 patient-years in patients with an HbA1c between 6% and 8%, and 6.3 per 100 patient-years in patients with an HbA1c >8%.

In the study population (n=1255), the mean age was 65.7 years (SD, 8.3 years), and 54% of the patients were male. The mean baseline HbA1c level was 6.7% (SD, 1.3%), with no significant difference between the atorvastatin and placebo groups. The baseline patient characteristics are shown in Table 1.

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The Figure, A, provides Kaplan–Meier curves for the time to sudden cardiac death (A) and all-cause mortality (B) in subgroups of patients according to baseline HbA1c levels (HbA1c ≤6% [reference group]; HbA1c >6% to ≤8%; HbA1c >8%).

### Table 1. Baseline Patient Characteristics, Presented Per HbA1c Category

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HbA1c, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤6</td>
</tr>
<tr>
<td>n</td>
<td>404</td>
</tr>
<tr>
<td>Age, y</td>
<td>66 (8)</td>
</tr>
<tr>
<td>Male, %</td>
<td>59.4</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.4 (0.4)</td>
</tr>
<tr>
<td>Atorvastatin treatment, %</td>
<td>48.3</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>145 (21)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>76 (11)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.9 (4.8)</td>
</tr>
<tr>
<td>Duration of diabetes, y</td>
<td>15.5 (8.4)</td>
</tr>
<tr>
<td>Time on dialysis, mo</td>
<td>7.8 (6.9)</td>
</tr>
<tr>
<td>Smoker/ex-smoker, %</td>
<td>43.6</td>
</tr>
<tr>
<td>CAD</td>
<td>29.2</td>
</tr>
<tr>
<td>CHF</td>
<td>31.9</td>
</tr>
<tr>
<td>History of Arrhythmia</td>
<td>18.1</td>
</tr>
</tbody>
</table>

#### Laboratory parameters

- **LDL cholesterol, mmol/L**: 3.2 (0.7) > 3.3 (0.8) > 3.3 (0.8)
- **Triglycerides, mmol/L**: 2.3 (1.5–3.5) > 2.5 (1.7–3.6) > 2.9 (1.9–4.5)
- **Hemoglobin, mmol/L**: 6.6 (0.8) > 6.8 (0.8) > 6.9 (0.9)
- **Albumin, g/L**: 38 (3) > 38 (3) > 38 (3)
- **C-reactive protein, mg/L**: 4.4 (2.0–11.4) > 5.2 (2.5–12.1) > 6.1 (2.6–15.7)
- **Calcium, mmol/L**: 2.3 (0.2) > 2.3 (0.2) > 2.3 (0.2)
- **Phosphate, mmol/L**: 1.9 (0.5) > 2.0 (0.5) > 1.9 (0.5)
- **Potassium, mmol/L**: 5.32 (0.9) > 5.14 (0.9) > 4.95 (0.7)

#### ECG characteristics

- **Sinus rhythm, %**: 91 > 89 > 86
- **AV block, %**: 7.4 > 7.7 > 5.3
- **QRS, left-axis type, %**: 60 > 63 > 71
- **Ventricular conduction defects, %**: 7 > 10 > 8
- **Repolarization disorder, %**: 62 > 61 > 70
- **LVH, %**: 12 > 12 > 14
- **QT interval, corrected, ms**: 423 (39) > 427 (39) > 426 (39)
- **Signs of MI, %**: 13 > 14 > 17
- **Atrial fibrillation/flutter, %**: 8 > 9 > 12

### Heart rate, bpm

- **Heart rate, bpm**: 78 (15) > 80 (16) > 79 (15)

BP indicates blood pressure; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; LDL, low-density lipoprotein; AV, atrioventricular; and LVH, left ventricular hypertrophy. Values are presented as mean (SD) or median (interquartile range) when appropriate. Study population n=1255.
sudden cardiac death per HbA1c category. Cox regression analyses pointed out the 2-fold increased hazards of sudden death in patients with an HbA1c >8% compared with those with normal HbA1c levels ≤6%, which persisted after the adjustment for confounders (Table 2). Evaluating potential intermediate conditions, we considered serum potassium; cardiac arrhythmia as documented by an ECG, left ventricular hypertrophy, and differences in the QRS axis (left-axis type); signs of MI; repolarization disorders; and corrected QT interval (Table 2). Adding any of the intermediate factors to the main model had little influence on the HRs for HbA1c. The additional adjustment for all intermediates together also did not materially affect the association of HbA1c with sudden death, suggesting that mechanisms other than the investigated ones largely explain the higher risk of sudden death at higher levels of HbA1c. When HbA1c was investigated as a continuous variable, the HR to experience sudden cardiac death increased significantly by 18% per unit (ie, 1%) increase in HbA1c (HR, 1.18; 95% CI, 1.05 to 1.32; Table 3). The association was even stronger after adjustment for confounders, showing a 21% greater hazard of sudden death per unit increase in HbA1c (HR, 1.21; 95% CI, 1.06 to 1.38).

Table 2. Baseline HbA1c and Risk of Sudden Death

<table>
<thead>
<tr>
<th>Model</th>
<th>HbA1c, %</th>
<th>≤6 (n=404)</th>
<th>&gt;6–≤8 (n=664)</th>
<th>&gt;8 (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Crude</td>
<td>1.69 (1.14–2.49)</td>
<td>0.008</td>
<td>9.16 (1.33–6.44)</td>
<td>0.002</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.82 (1.20–2.77)</td>
<td>0.005</td>
<td>2.25 (1.32–3.81)</td>
<td>0.003</td>
</tr>
<tr>
<td>Adjusted* plus CAD and CHF (main model)</td>
<td>1.85 (1.22–2.81)</td>
<td>0.004</td>
<td>2.26 (1.33–3.85)</td>
<td>0.003</td>
</tr>
<tr>
<td>Main model plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>1.90 (1.25–2.89)</td>
<td>0.003</td>
<td>2.35 (1.38–4.01)</td>
<td>0.002</td>
</tr>
<tr>
<td>Rhythm disorders</td>
<td>1.84 (1.21–2.80)</td>
<td>0.004</td>
<td>2.23 (1.31–3.79)</td>
<td>0.003</td>
</tr>
<tr>
<td>LVH and QRS, left-axis type</td>
<td>1.86 (1.23–2.83)</td>
<td>0.004</td>
<td>2.18 (1.28–3.72)</td>
<td>0.004</td>
</tr>
<tr>
<td>Signs of MI</td>
<td>1.85 (1.22–2.80)</td>
<td>0.004</td>
<td>2.25 (1.32–3.84)</td>
<td>0.003</td>
</tr>
<tr>
<td>Repolarization disorders</td>
<td>1.86 (1.22–2.83)</td>
<td>0.004</td>
<td>2.20 (1.29–3.76)</td>
<td>0.004</td>
</tr>
<tr>
<td>All intermediate factors</td>
<td>1.89 (1.24–2.89)</td>
<td>0.003</td>
<td>2.20 (1.29–3.78)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; CHF, congestive heart failure; and LVH, left ventricular hypertrophy. Study population n=1255.

*Adjustments were made for age, sex, atorvastatin treatment, systolic blood pressure, duration of diabetes, time on dialysis, smoking status, body mass index, levels of low-density lipoprotein cholesterol, triglycerides, albumin, hemoglobin, calcium, phosphate, and C-reactive protein. In the main model, further adjustments were made for the presence of coronary artery disease (as defined by history of MI, coronary artery bypass grafting surgery, percutaneous coronary intervention, or coronary heart disease documented by coronary angiography) and the presence of congestive heart failure. QT interval and corrected QT interval were analyzed separately because of missing values and had no impact on the association of HbA1c with sudden death.

Table 3. Absolute Rates of Sudden Death, MI, Stroke, the Primary End Point, All-Cause Mortality, Heart Failure Death, and Mortality Except for Sudden Death, Plus HRs With 95% CIs per Unit Increase in HbA1c as a Continuous Variable; n=1255

<table>
<thead>
<tr>
<th>Events</th>
<th>Sudden Death</th>
<th>MI</th>
<th>Stroke</th>
<th>Primary End Point*</th>
<th>All-Cause Mortality</th>
<th>Heart Failure Death</th>
<th>Mortality Except for Sudden Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, person-y</td>
<td>160</td>
<td>200</td>
<td>103</td>
<td>469</td>
<td>617</td>
<td>41</td>
<td>457</td>
</tr>
<tr>
<td>Incidence rate/100 person-y</td>
<td>4.5</td>
<td>5.9</td>
<td>3.0</td>
<td>14.3</td>
<td>17.4</td>
<td>1.2</td>
<td>12.9</td>
</tr>
<tr>
<td>HbA1c crude HR (95% CI)</td>
<td>1.18 (1.05–1.32)</td>
<td>0.98 (0.87–1.09)</td>
<td>1.13 (0.98–1.31)</td>
<td>1.08 (1.01–1.16)</td>
<td>1.08 (1.02–1.15)</td>
<td>1.14 (0.91–1.43)</td>
<td>1.05 (0.98–1.13)</td>
</tr>
<tr>
<td>HbA1c adjusted HR† (95% CI)</td>
<td>1.21 (1.06–1.38)</td>
<td>0.94 (0.83–1.07)</td>
<td>1.11 (0.93–1.32)</td>
<td>1.09 (1.01–1.18)</td>
<td>1.09 (1.02–1.17)</td>
<td>1.30 (1.00–1.68)</td>
<td>1.04 (0.96–1.13)</td>
</tr>
</tbody>
</table>

Study population n=1255.

*The primary end point was a composite of death resulting from cardiac causes, fatal stroke, nonfatal MI, or nonfatal stroke, whichever occurred first.
†Adjustments were made for age, sex, atorvastatin treatment, systolic blood pressure, duration of diabetes, time on dialysis, smoking status, body mass index, levels of low-density lipoprotein cholesterol, triglycerides, albumin, hemoglobin, calcium, phosphate, C-reactive protein, the presence of coronary artery disease (as defined by history of myocardial infarction, coronary artery bypass grafting surgery, percutaneous coronary intervention, or coronary heart disease documented by coronary angiography), and the presence of congestive heart failure.
pared with patients in the first quartile (HR for third quartile, 2.00 [95% CI, 1.24 to 3.23]; HR for fourth quartile, 1.83 [95% CI, 1.11 to 3.03]).

Baseline HbA1c and Risk of MI, Stroke, and the Primary End Point of Combined CVE and Death Resulting From Heart Failure

Investigating further cardiac and vascular outcomes, we found no association of HbA1c with the risk of MI. In both continuous (adjusted HR, 0.94; 95% CI, 0.83 to 1.07) and categorical analyses, the risk of MI did not increase (Tables 3 through 5). When nonfatal MI and fatal MI were analyzed separately, the results were similar, showing no relation to HbA1c.

Higher levels of HbA1c by trend affected the risk of stroke but not significantly. Similarly, higher effect estimates for death resulting from heart failure were observed with higher levels of HbA1c; however, the CIs were wide (Tables 3 through 5).

The primary end point of combined CVE was markedly increased with higher levels of HbA1c (Table 3). Patients with an HbA1c >8% had an adjusted 37% higher risk of experiencing a CVE compared with patients with an HbA1c ≤6%.

This relation was explained mainly by the impact of HbA1c on sudden cardiac death because no association was found for CVE except sudden death.

To strengthen our results, we eliminated any potential influence by atorvastatin treatment and repeated all analyses in the placebo group only. The results were similar, indicating no interaction and supporting the use of the complete data.

Baseline HbA1c and Risk of All-Cause Mortality

In univariate analyses, all-cause mortality increased by 8% per unit increase in HbA1c (HR, 1.08; 95% CI, 1.02 to 1.15; Table 3). Multivariable adjustment resulted in an HR of 1.09 (95% CI, 1.02 to 1.17). The results of categorical analyses are shown in Tables 4 and 5 and the Figure, B. Patients with an HbA1c >6% were 34% more likely to die, as were those with

### Table 4. HRs and 95% CIs for Sudden Cardiac Death, MI, Stroke, and the Primary End Point According to Categories of HbA1c at Baseline

<table>
<thead>
<tr>
<th>Model</th>
<th>HbA1c</th>
<th>Sudden Death</th>
<th>MI</th>
<th>Stroke</th>
<th>Primary End Point*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Crude</td>
<td>≤6</td>
<td>1.00 (0.77–1.31)</td>
<td>0.814</td>
<td>1.58 (0.98–2.54)</td>
<td>0.058</td>
</tr>
<tr>
<td></td>
<td>&gt;6–≤8</td>
<td>1.69 (1.14–2.49)</td>
<td>0.008</td>
<td>1.58 (0.98–2.54)</td>
<td>0.058</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>2.14 (1.33–3.44)</td>
<td>0.002</td>
<td>1.74 (0.96–3.18)</td>
<td>0.070</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>≤6</td>
<td>1.00 (0.77–1.31)</td>
<td>0.814</td>
<td>1.58 (0.98–2.54)</td>
<td>0.058</td>
</tr>
<tr>
<td></td>
<td>&gt;6–≤8</td>
<td>1.85 (1.22–2.81)</td>
<td>0.004</td>
<td>1.56 (0.93–2.62)</td>
<td>0.093</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>2.26 (1.33–3.85)</td>
<td>0.003</td>
<td>1.67 (0.84–3.30)</td>
<td>0.142</td>
</tr>
</tbody>
</table>

Study population n=1255.

*The primary end point was a composite of death resulting from cardiac causes, fatal stroke, nonfatal MI, or nonfatal stroke, whichever occurred first.

†Adjustments were made for age, sex, atorvastatin treatment, systolic blood pressure, duration of diabetes, time on dialysis, smoking status, body mass index, levels of low-density lipoprotein cholesterol, triglycerides, albumin, hemoglobin, calcium, phosphate, C-reactive protein, the presence of coronary artery disease (as defined by history of MI, coronary artery bypass grafting surgery, percutaneous coronary intervention, or coronary heart disease documented by coronary angiography), and the presence of congestive heart failure.

### Table 5. HRs and 95% CIs for All-Cause Mortality, Heart Failure Death, and Mortality Except for Sudden Cardiac Death According to Categories of HbA1c at Baseline

<table>
<thead>
<tr>
<th>Model and HbA1c Level</th>
<th>All-Cause Mortality</th>
<th>Heart Failure Death</th>
<th>Mortality Except for Sudden Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Crude</td>
<td>≤6</td>
<td>1.00 (0.77–1.31)</td>
<td>0.814</td>
</tr>
<tr>
<td></td>
<td>&gt;6–≤8</td>
<td>1.69 (1.14–2.49)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>2.14 (1.33–3.44)</td>
<td>0.002</td>
</tr>
<tr>
<td>Adjusted†</td>
<td>≤6</td>
<td>1.00 (0.77–1.31)</td>
<td>0.814</td>
</tr>
<tr>
<td></td>
<td>&gt;6–≤8</td>
<td>1.85 (1.22–2.81)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>&gt;8</td>
<td>2.26 (1.33–3.85)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Study population n=1255.

*Adjustments were made for age, sex, atorvastatin treatment, systolic blood pressure, duration of diabetes, time on dialysis, smoking status, body mass index, levels of low-density lipoprotein cholesterol, triglycerides, albumin, hemoglobin, calcium, phosphate, C-reactive protein, the presence of coronary artery disease (as defined by history of MI, coronary artery bypass grafting surgery, percutaneous coronary intervention, or coronary heart disease documented by coronary angiography), and the presence of congestive heart failure.
an HbA1c >8%, compared with patients with normal HbA1c levels ≤6%.

Additional analyses revealed that the association of HbA1c with all-cause mortality was explained mainly by its effect on sudden cardiac death. No association was seen for mortality except for sudden death (Tables 3 through 5).

Discussion
We analyzed data from 1255 hemodialysis patients with T2DM who took part in the 4D Study and experienced a high incidence of prespecified and centrally adjudicated end points. In the present analysis, baseline HbA1c was a strong risk factor for sudden cardiac death during 4 years of follow-up. In patients with an HbA1c >8%, the risk of dying suddenly was more than 2-fold increased compared to those with an HbA1c <6%. There was a trend for higher risks of stroke and deaths resulting from heart failure, whereas MI was not affected. Both combined CVE and mortality were increased at higher levels of HbA1c, a finding that was explained mainly by the impact of HbA1c on sudden death.

When enrolling in the 4D Study, patients had an average history of known diabetes mellitus for 18 years and had been on maintenance hemodialysis for an average of 8 months. They had a significant burden of microangiopathic complications (diabetic retinopathy, 71%; polyneuropathy, 60%) and macroangiopathic complications (about one third of these patients had coronary artery disease at baseline). Sudden death accounted with 26%, the highest proportion of deaths in the 4D Study; only 11% of deaths were attributed to MI and adjudicated coronary heart disease. Similar information was reported from the US Renal Data System, which showed that 27% of deaths in dialysis patients had been classified as cardiac arrest or cardiac arrhythmia, and only 8% were classified as deaths resulting from acute MI and atherosclerotic heart disease. A number of different causes may account for sudden death in dialysis patients, including microvascular and macrovascular disease, sympathetic overactivity, structural heart disease, cardiac fibrosis, and electrolyte and volume shifts resulting from the hemodialysis procedure. Our present study adds glycemic control to the list, which raises the question of potential mechanisms.

Hyperglycemia has been shown to play a significant role in the development of microangiopathy, endothelial dysfunction, and impaired myocardial vasodilator function, which contribute to cardiac microvessel disease and structural heart disease. It has been reported that hyperglycemia induced excess generation of highly reactive free radicals, causing oxidative stress, and inflammatory cytokines. In this context, it is important to note that HbA1c is presumably an indicator of a higher load of the Amadori-derived advanced glycation end products, which are known to exert and amplify oxidative stress and can be a consequence of oxidative stress. These Amadori-derived advanced glycation end product toxins are profibrotic and directly involved in the pathogenesis of the inflammatory response syndrome and vascular complications.

Myocardial fibrosis has mechanical and electrical sequelae that affect cardiovascular prognosis. It reduces the ventricular compliance and promotes arrhythmia by causing local delay in the spread of the action potential. In an animal model of mild diabetes mellitus, researchers observed an enhanced susceptibility to ventricular arrhythmias, with increased electrophysiological sensitivity to catecholamines and nonhomogeneous collagen accumulation affecting local conduction. Studies in diabetic patients found regional cardiac denervation and sympathetic overactivity, potentially resulting in life-threatening myocardial electrical instability. In line with these findings, HbA1c was reported to be a predictor of spontaneous ventricular arrhythmias in diabetic patients with an implantable cardioverter-defibrillator. We further found HbA1c to be a risk factor for all-cause mortality, which is in line with previous studies in diabetic patients from the general population. For chronic kidney disease patients, the literature is not unequivocal. Although several studies reported lower survival rates for diabetic patients with poor glycemic control, another study in 24 875 maintenance hemodialysis patients from the Fresenius dialysis clinics in the United States did not indicate any association between HbA1c and 1-year survival. Although the lack of a survival association in this study could have been due to the short-term follow-up and further methodological differences, this study has led to some confusion about the role of glycemic control in dialysis patients. Data from 23 618 patients in the DaVita outpatient clinics over 3 years showed in unadjusted survival analyses paradoxically lower death HRs with higher HbA1c values. However, after adjustment for a large number of potential confounders, higher HbA1c values were incrementally associated with higher death risks, and lower HbA1c levels not related to malnutrition or anemia appeared to be associated with improved survival.

Surprisingly, in patients without renal failure, treatment that improved glycemic control did not achieve the predicted benefit in recent trials with regard to macrovascular complications. In fact, the question arose whether tight glycemic control might even increase the risk of death, bringing the role of glycemic control as a risk factor into question. In this context, distinguishing between microvascular and macrovascular complications is of special interest. Importantly, the risk of MI as a major macrovascular complication was not affected by glycemic control in our study. There was also no convincing effect on stroke, which is thought to result from both macrovascular and microvascular components in diabetic patients. These observations are in line with results from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, which showed that the beneficial effect of intensive glycemic control was achieved mainly by the reduction of microvascular complications, whereas macrovascular events alone could not be reduced significantly. However, macrovascular events, predominantly MI, account for the majority of deaths in diabetic patients in the general population, possibly explaining in part why the intervention trials did not show a reduction in all-cause death. In contrast, patients with renal disease experience a strikingly different risk pattern, with a high proportion of sudden cardiac deaths and atherosclerotic deaths playing only a minor role. Although the effect of tight glycemic control on macrovas-
cular complications is still under debate, its effect on microvascular complications has repeatedly been shown. Further studies will clarify whether better glucose control may decrease the risk of sudden cardiac death in dialysis patients.

This study had certain limitations. It was a posthoc analysis within a selected cohort of German patients with T2DM on hemodialysis. Therefore, the relationship between HbA1c and risk may not be generalizable to other patient populations. HbA1c measurement in patients on hemodialysis treatment might have been compromised by reduced red blood cell lifespan and the widespread use of erythropoietin, increasing the proportion of reticulocytes and younger red blood cells with less time for glycosylation to occur. This may have led to an underestimation of HbA1c levels, but because of its general nature, it is unlikely to have influenced our results, which were based on comparisons within the same study population. The analysis of specific outcomes, especially sudden cardiac death, and their association with HbA1c was the main strength of this study. In this context, the long-term follow-up, adequate sample size, and high incidence of prespecified and centrally adjudicated end points are additional strengths.

Conclusions
Glycemic control as represented by the level of HbA1c was strongly associated with sudden cardiac death in hemodialyzed type 2 diabetic patients. Although MI was not affected, the risks of the combined primary end point and mortality increased significantly at higher levels of HbA1c and were explained mainly by the impact of glycemic control on sudden cardiac death. Whether tight glucose control decreases the risk of sudden death without causing side effects should be examined in future trials.

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We thank all the investigators and study nurses who participated in the 4D Study; without their collaboration, this article would not have been written. Special thanks go to the laboratory staff at the universities of Freiburg, Heidelberg, and Würzburg, especially Silke Dietz and Katja Blouin. We also thank clinical epidemiologists Dr Friedo Dekker for discussions and Dr Diana Grooendorst for advise and critical proofreading of the manuscript.

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Disclosures
None.

References
Cardiac disease represents the leading cause of death, particularly sudden cardiac death. Evidence suggests that poor glycemic control may affect the arrhythmogenesis of patients with kidney failure because it affects the development of comorbidities, electrolyte balance, function of potassium and calcium channels, and sympathetic activity. In the present study of 1255 hemodialysis patients with type 2 diabetes mellitus, poor glycemic control as represented by elevated levels of glycohemoglobin $A_1c$ ($HbA_1c$) was associated with an increased risk of sudden cardiac death. Patients with an $HbA_1c > 8\%$ had a 2-fold higher risk of sudden death compared with those with an $HbA_1c \leq 6\%$ independently of other known risk factors. Although myocardial infarction was not affected, the risks of the combined primary end point and mortality significantly increased at higher levels of $HbA_1c$, and were explained mainly by the impact of glycemic control on sudden cardiac death. By pointing out the importance of distinguishing the pathophysiologically different causes of death, the present study offers new perspectives for future research on glucose control in populations with a high incidence of sudden death. Importantly, these results may suggest novel therapeutic strategies in diabetic hemodialysis patients, in whom sudden cardiac death accounts for a quarter of all deaths. Whether tight glucose control decreases the risk of sudden death without causing side effects remains to be studied.
Glycemic Control and Cardiovascular Events in Diabetic Hemodialysis Patients
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