Metabolic alterations in dialysis patients

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CHAPTER 4

Glycemic control and cardiovascular events in diabetic hemodialysis patients

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Abstract

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: Glycated hemoglobin 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 for a median of 4 years. By Cox regression analyses, we determined hazard ratios to reach pre-specified, adjudicated endpoints according to HbA1c levels at baseline: sudden cardiac death (SD; n=160), myocardial infarction (MI, n=200), stroke (n=103), cardiovascular events (CVE; n=469), death due to 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 a HbA1c >8% had a more than 2fold higher risk of sudden death compared to those with a HbA1c ≤6% (hazard ratio 2.14; 95% confidence interval 1.33-3.44), persisting in multivariate models. Per 1% increase in HbA1c, the risk of sudden death significantly rose by 18%, and similarly, CVE and mortality increased by 8%, respectively. There was a trend for higher risks of stroke and deaths due to heart failure, while myocardial infarction was not affected. Both, the increased risks of CVE and mortality were mainly explained 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 CVE and mortality. In contrast, myocardial infarction was not affected. Whether interventions achieving tight glycemic control decrease sudden death, requires further evaluation.

Introduction

The rate of death of dialysis patients is abysmal. The ERA-EDTA registry reports a 18% first year mortality rate[1], whereas the USRDS reports an even higher annual mortality rate of >20% [2]. Cardiac disease represents with 41% the leading cause of death among dialysis patients[2]. The major occurring event is sudden cardiac death, which as a single cause accounts for 26-27% 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, in order to develop interventional strategies and reduce the excess mortality of these patients.

Diabetes mellitus is a growing health problem, and a risk factor for the development and progression of chronic kidney disease (CKD). Almost one half of the US dialysis patients developed end-stage renal disease (ESRD) due to type 2 diabetes mellitus (T2DM)[2]. These patients have a higher co-morbidity and poorer outcome as compared to non diabetic patients on dialysis[2], as reflected by a five year survival of only 35%[4].

Poor glycemic control is associated with the development of comorbidities including coronary artery disease and myocardial infarction in the general population[5, 6]. It has been shown that these are predisposing conditions for sudden cardiac death[7]. Glycemia is furthermore 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.

To that end, we investigated the association of hemoglobin A1c (HbA1c) with the risk of sudden cardiac death, myocardial infarction, stroke, combined cardiovascular events, death due to heart failure, and all-cause mortality in hemodialysis patients. We analyzed data from the German Diabetes Dialysis Study (4D Study: Die Deutsche Diabetes Dialyse Studie), which evaluated atorvastatin in 1255 patients with T2DM on maintenance hemodialysis[3].

Materials and 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, age 18 – 80 years, and on hemodialysis for less than 2 years. Between March 1998 and October 2002, patients were recruited in 178 dialysis centres in Germany. After a period of 4 weeks, patients were randomly assigned to double-blinded treatment with either 20mg atorvastatin (n=619) or placebo (n=636) once daily. Study visits took place three times before randomization (visit 1-3), at randomization (visit 4), and at four weeks (visit 5) and every six months (visit 6 etc.) after randomization until the date of death, censoring, or end of the study in March 2004. The primary endpoint of the 4D study was defined as a composite of death from cardiac causes, fatal or nonfatal stroke and nonfatal myocardial infarction (MI), whichever occurred first (composite cardiovascular endpoint; CVE). Death from cardiac causes comprised sudden death, fatal MI, death due to congestive heart failure, death due to coronary heart disease during or within 28 days after an intervention, and all other deaths ascribed to coronary heart disease. Sudden death was considered as: death as verified by terminal rhythm disorders in an electrocardiogram; by witnesses observed death within one hour after the onset of cardiac symptoms; confirmed by autopsy; unexpected death, presumably or possibly of cardiac origin and in the absence of a potassium level greater or equal to 7.5 mmol per liter before the start of the three most recent sessions of hemodialysis. Myocardial infarction was diagnosed when two of the following three criteria were met: typical symptoms, elevated levels of cardiac enzymes (i.e. a level of creatine kinase MB above 5 percent 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 greater than 2 ng per milliliter), or diagnostic changes on the electrocardiogram. When death occured within 28 days after a MI as diagnosed above, it was specified as death due to MI. The classifications were made exclusively with fatal MI only being classified as MI deaths, and not sudden cardiac deaths. 4D Study endpoints were centrally adjudicated by three

members of the endpoint committee blinded to study treatment and according to pre-defined criteria.

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

Data collection

Information on age, gender 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 (CAD) and congestive heart failure (CHF), as well as the duration of diabetes mellitus and dialysis treatment were reported by the patients´ nephrologists. Coronary artery disease was defined by the 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 sitting position. Body mass index (BMI) 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, Germany. HbA1c was measured in blood samples taken at baseline at study visit 3 (1 week before randomization), using high performance liquid chromatography[12]. Inter-assay coefficients of variance were <5%. All blood samples were taken before the start of dialysis sessions and administration of drugs.

Statistical Analysis

Continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR) as appropriate, and categorical variables were expressed as percentages.

The study population was divided into three groups, according to HbA1c levels at baseline: normal ≤6%, elevated >6% ≤8%, high >8%. First, we assessed the association of baseline HbA1c with sudden death both as continuous and as

categorical variable. For the latter, the patients with a HbA1c ≤6% were used as the reference group. Absolute (incidence) rates were calculated as the number of events occuring per 100 person years of follow-up. Kaplan-Meier curves were performed in each HbA1c group, and the log rank test was computed to compare curves. By Cox regression analyses, hazard ratios and corresponding 95% confidence intervals 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, BMI, levels of LDL-cholesterol, triglycerides, albumin, haemoglobin, calcium, phosphate, C-reactive protein, and for the presence of CAD and CHF (main model). Second, we performed additional Cox regression analyses with inclusion of potassium and electrocardiographic variables, which may represent intermediate conditions lying in the causal pathway of the effect of glycemic control on sudden death. The variables were included one at a time in order to see the magnitude, by which the effect estimate for the risk of HbA1c on sudden death changed, respectively. Furthermore, In an analysis aiming for the impact of all intermediate variables together, they were simultaneously added to the main model. Third, we investigated HbA1c and the risk of other adverse cardiac and vascular outcomes including MI, stroke, the combined primary endpoint (CVE), and death due to heart failure, to distinguish whether potential effects of glycemic control are specific for sudden death, or generally influencing cardiac and vascular outcomes. In order to see whether a potential impact on the primary endpoint is mainly explained through the effect of HbA1c on sudden death, we also assessed the risks of HbA1c on CVE except for sudden death. Fourth, we similarly determined the association of HbA1c with all-cause mortality, and assessed the risks of HbA1c on all deaths except for sudden death. Finally, to test the robustness of our results, we divided the study population into quartiles of HbA1c at baseline, and repeated our analyses on the effect of glycemic control on all outcomes using this alternative categorization of HbA1c. We furthermore repeated all analyses in the placebo group only, in order to eliminate any potential influence by atorvastatin treatment. All p-values are reported two-sided. Analyses were performed using SPSS version 16.0. The authors had full access to the data and take responsibility for its integrity. 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 a HbA1c 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 endpoint of CVE. A total of 617 patients died, of whom 160 patients died of sudden cardiac death. Furthermore, 41 patients died due to congestive heart failure, 200 patients experienced a MI (fatal or non-fatal), and 103 patients experienced a stroke (fatal or non-fatal).

In the study population (n=1255), the mean (SD) age was 65.7 (8.3) years, and 54% of the patients were male. The mean (SD) baseline HbA1c level was 6.7 (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 increasing over the categories of HbA1c: 3.0 per 100 person years (py) in the group with HbA1c ≤6%, 5.0/100py in patients with a HbA1c between 6 and 8%, and 6.3/100py in patients with a HbA1c >8%. Figure 1A provides Kaplan-Meier curves for the time to sudden cardiac death per HbA1c category. Cox regression analyses pointed out the twice as high hazards of sudden death in patients with a HbA1c >8% as compared to 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 electrocardiogram (ECG), left ventricular hypertrophy and differences in QRS axis (left axis type), signs of MI, repolarisation disorders, and corrected QT interval (Table 2). Adding any of the intermediate factors to the main model had little influence on the hazard ratios for HbA1c. The additional adjustment for all intermediates together also did not materially impact on the association of HbA1c with sudden death, suggesting mechanisms other than the investigated

ones to largely explain the higher risk of sudden death at higher levels of HbA1c. Investigating HbA1c as a continuous variable, the hazard to experience sudden cardiac death increased significantly by 18% per unit (i.e. 1%) increase in HbA1c (hazard ratio (HR) 1.18, 95% confidence interval (CI) 1.05-1.32, 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 1.06-1.38).

Additional analyses using quartiles of HbA1c (≤5.8%, >5.8 to ≤6.6%, >6.6 to ≤7.4%, >7.4%) showed similar results: Patients of the third and fourth HbA1c quartile had significantly increased risks of sudden cardiac death as compared to patients of the first quartile ($HR_{3rd\ quartile}$ 2.00, 95% CI 1.24-3.23; $HR_{4th\ quartile}$ 1.83, 95% CI 1.11-3.03, respectively).

Baseline HbA1c and risk of myocardial infarction, stroke, the primary endpoint of combined cardiovascular events and death due to heart failure

Investigating further cardiac and vascular outcomes, we found no association of HbA1c with the risk of MI. Both in continuous (adjusted HR 0.94, 95% CI 0.83-1.07) and in categorical analyses, the risk of MI did not increase (Tables 3 and 4). When non-fatal and fatal MI were analyzed separately, the results were similar showing no relation to HbA1c.

Higher levels of HbA1c by trend, but not significantly, affected the risk of stroke. Similarly, higher effect estimates for death due to heart failure were observed with higher levels of HbA1c, however the confidence intervals were wide (Tables 3 and 4).

The primary endpoint of combined CVE was markedly increased with higher levels of HbA1c (Table 3). Patients with a HbA1c >8% had an adjusted 37% higher risk of experiencing a CVE as compared to patients with a HbA1c ≤6%. This relation was mainly explained by the impact of HbA1c on sudden cardiac death, since 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.

Table 1: Baseline patient characteristics, presented per HbA1c* category; study population n=1255

Characteristic	HbA1c (%)		
	≤ 6 (n=404)	> 6 ≤ 8 (n=664)	> 8 (n=187)
Age *years*	66 (8)	66 (8)	65 (9)
Gender *% men*	59.4	50.9	52.9
HbA1c *%*	5.4 (0.4)	6.9 (0.5)	8.9 (0.8)
Atorvastatin treatment *%*	48.3	51.5	52.9
Systolic BP* *mmHg*	145 (21)	147 (22)	144 (23)
Diastolic BP *mmHg*	76 (11)	76 (11)	76 (11)
BMI* kg/m^2	26.9 (4.8)	27.7 (4.8)	28.2 (4.8)
Duration of diabetes *years*	15.5 (8.4)	18.9 (8.9)	20.9 (8.1)
Time on dialysis *months*	7.8 (6.9)	8.2 (6.9)	9.6 (6.8)
Smoker / Ex-smoker *%*	43.6	37.8	42.8
Arrhythmia *%*	18.1	19.0	19.8
History of			
CAD* *%*	29.2	29.4	29.9
CHF* *%*	31.9	36.7	38.0
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 (2.8-15.7)
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
Repolarisation 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*	78 (15)	80 (16)	79 (15)

Values are presented as means (SD) or median (interquartile range) or %.
*Abbreviations: HbA1c = hemoglobin A1c; BP = blood pressure;
BMI = body mass index; CAD = coronary artery disease,
CHF = congestive heart failure; LDL = low density lipoprotein,
ECG = electrocardiogram (resting), AV = atrio – ventricular,
LVH = left ventricular hypertrophy, MI = myocardial infarction.

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 1.02-1.15; Table 3). Multivariable adjustment resulted in a hazard ratio of 1.09 (95% CI 1.02-1.17). The results of categorical analyses are shown in Table 4 and Figure 1B. Patients with a HbA1c >6% were 34% more likely to die, as were those with a HbA1c >8%, compared to patients with normal HbA1c levels ≤6%.

Additional analyses revealed that the association of HbA1c with all-cause mortality was mainly explained by its effect on sudden cardiac death, since no association was seen for mortality except for sudden death (Tables 3 and 4).

Table 2: Baseline HbA1c* and the risk of sudden death; study population n=1255

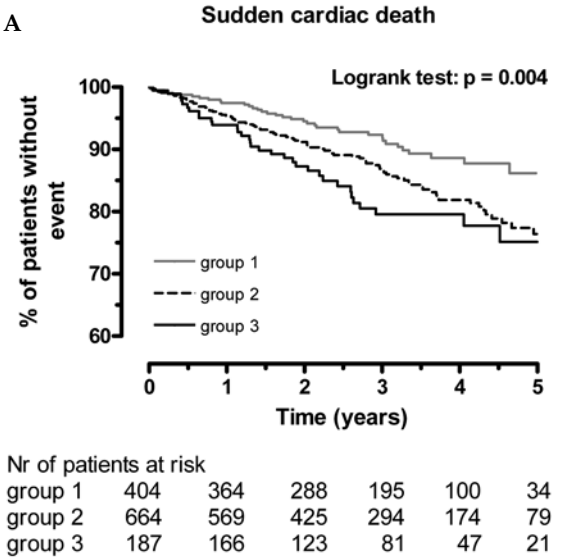
	HbA1c (%)				
	≤ 6 (n=404)	> 6 ≤ 8 (n=664)		> 8 (n=187)	
Model		HR (95% CI)	p	HR (95% CI)	p
Crude	1	1.69 (1.14-2.49)	0.008	2.14 (1.33-3.44)	0.002
Adjusted†	1	1.82 (1.20-2.77)	0.005	2.25 (1.32-3.81)	0.003
Adjusted† + CAD*, CHF* (main model)	1	1.85 (1.22-2.81)	0.004	2.26 (1.33-3.85)	0.003
Main model plus					
Potassium	1	1.90 (1.25-2.89)	0.003	2.35 (1.38-4.01)	0.002
Rhythm disorders	1	1.84 (1.21-2.80)	0.004	2.23 (1.31-3.79)	0.003
LVH*, QRS left axis type	1	1.86 (1.23-2.83)	0.004	2.18 (1.28-3.72)	0.004
Signs of MI*	1	1.85 (1.22-2.80)	0.004	2.25 (1.32-3.84)	0.003
Repolarisation disorders	1	1.86 (1.22-2.83)	0.004	2.20 (1.29-3.76)	0.004
All intermediate factors	1	1.89 (1.24-2.89)	0.003	2.20 (1.29-3.78)	0.004

*Abbreviations: HbA1c = hemoglobin A1c; CAD = coronary artery disease, CHF = congestive heart failure; K= Potassium
LVH = left ventricular hypertrophy, MI = myocardial infarction.

†Adjusted: Adjustments were made for age, sex, atorvastatin treatment, systolic blood pressure, duration of diabetes, time on dialysis, smoking status, body mass index, levels of LDL-cholesterol, triglycerides, albumin, hemoglobin, calcium, phosphate and C-reactive protein.

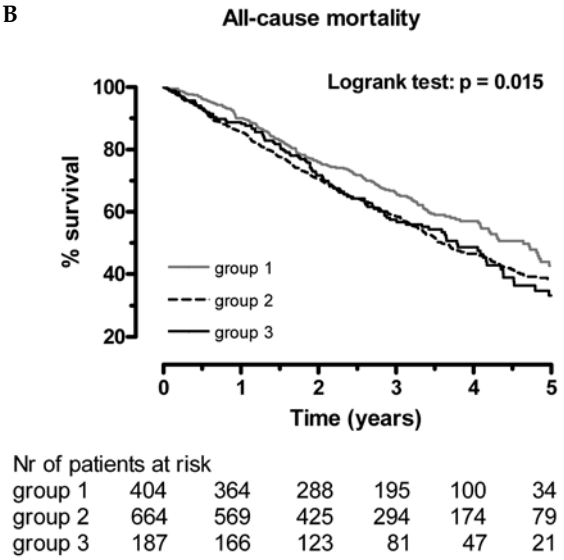
Main model: further adjustments were made for the presence of coronary artery disease (as defined by history of myocardial infarction, coronary artery bypass grafting surgery, percutaneous coronary intervention, coronary heart disease documented by coronary angiography), and the presence of congestive heart failure.

QT interval and corrected QT interval were analyzed separately due to missing values and had no impact in the association of HbA1c with sudden death.



Nr of patients at risk

group 1	404	364	288	195	100	34
group 2	664	569	425	294	174	79
group 3	187	166	123	81	47	21



Nr of patients at risk

group 1	404	364	288	195	100	34
group 2	664	569	425	294	174	79
group 3	187	166	123	81	47	21

Figure 1A-B: Kaplan Meier curves for the time to A) sudden cardiac death, B) all-cause mortality in subgroups of patients according to baseline hemoglobin A1c (HbA1c) levels (group1: HbA1c ≤6% (=reference group), group 2: HbA1c >6 ≤8%, group 3: HbA1c >8%).

Table 3: Absolute rates of sudden death, myocardial infarction (MI), stroke, the primary endpoint, all-cause mortality, heart failure death and mortality except for sudden death, and hazard ratios with 95% confidence intervals (HR, 95% CI) per unit increase in HbA1c as continuous variable; n=1255

	Sudden death	MI	stroke	Primary endpoint*
events	160	200	103	469
Person-years (py)	3555	3368	3465	3287
Incidence rate / 100 py	4.5	5.9	3.0	14.3
HbA1c crude HR (95%CI)	1.18 (1.05-1.32)	0.98 (0.87-1.09)	1.13 (0.98-1.31)	1.08 (1.01-1.16)
HbA1c adj. HR[1] (95%CI)	1.21 (1.06-1.38)	0.94 (0.83-1.07)	1.11 (0.93-1.32)	1.09 (1.01-1.18)

	All-cause mortality	Heart failure death	Mortality except for sudden death
events	617	41	457
Person-years (py)	3555	3555	3555
Incidence rate / 100 py	17.4	1.2	12.9
HbA1c crude HR (95%CI)	1.08 (1.02-1.15)	1.14 (0.91-1.43)	1.05 (0.98-1.13)
HbA1c adj. HR[1] (95%CI)	1.09 (1.02-1.17)	1.30 (1.00-1.68)	1.04 (0.96-1.13)

[1]Adjusted: Adjustments were made for age, sex, atorvastatin treatment, systolic blood pressure, duration of diabetes, time on dialysis, smoking status, body mass index, levels of LDL-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, coronary heart disease documented by coronary angiography), and the presence of congestive heart failure.

*The primary endpoint was a composite of death from cardiac causes, fatal stroke, non-fatal myocardial infarction, or non-fatal stroke, whichever occurred first.

Table 4: Hazard ratios and 95% confidence intervals (HR, 95% CI) for sudden cardiac death, myocardial infarction (MI), stroke, the primary endpoint, death due to heart failure, all-cause mortality, and mortality except for sudden cardiac death according to categories of HbA1c at baseline; n=1255

		Sudden death		MI		Stroke		Primary endpoint*	
model	HbA1c	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
crude	≤6	1		1		1		1	
	>6≤8	1.69 (1.14-2.49)	0.008	1.04 (0.77-1.41)	0.814	1.58 (0.98-2.54)	0.058	1.29 (1.04-1.59)	0.019
	>8	2.14 (1.33-3.44)	0.002	0.80 (0.50-1.28)	0.358	1.74 (0.96-3.18)	0.070	1.32 (0.99-1.75)	0.056
Adj[1]	≤6	1		1		1		1	
	>6≤8	1.85 (1.22-2.81)	0.004	0.94 (0.68-1.30)	0.707	1.56 (0.93-2.62)	0.093	1.31 (1.05-1.65)	0.018
	>8	2.26 (1.33-3.85)	0.003	0.77 (0.47-1.26)	0.299	1.67 (0.84-3.30)	0.142	1.37 (1.00-1.87)	0.050
		All-cause mortality		Heart failure death		Mortality except for sudden death			
crude	≤6	1		1		1			
	>6≤8	1.29 (1.07-1.55)	0.006	1.34 (0.65-2.75)	0.427	1.19 (0.97-1.47)	0.098		
	>8	1.31 (1.02-1.68)	0.033	1.44 (0.56-3.71)	0.452	1.10 (0.82-1.47)	0.543		
Adj[1]	≤6	1		1		1			
	>6≤8	1.34 (1.10-1.63)	0.004	1.53 (0.70-3.33)	0.288	1.19 (0.96-1.50)	0.117		
	>8	1.34 (1.02-1.76)	0.039	2.12 (0.75-5.98)	0.155	1.10 (0.80-1.52)	0.546		

Adjusted[1]: Adjustments were made for age, sex, atorvastatin treatment, systolic blood pressure, duration of diabetes, time on dialysis, smoking status, body mass index, levels of LDL-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, coronary heart disease documented by coronary angiography), and the presence of congestive heart failure.

*The primary endpoint was a composite of death from cardiac causes, fatal stroke, non-fatal myocardial infarction, or non-fatal stroke, whichever occurred first.

Discussion

We analyzed data from 1255 hemodialysis patients with type 2 diabetes mellitus who took part in the 4D Study and experienced a high incidence of pre-specified and centrally adjudicated endpoints. In the present analysis, baseline HbA1c was a strong risk factor for sudden cardiac death during 4 years of follow-up. In patients with a HbA1c above 8 percent, the risk of dying suddenly was more than twice as high than in those with a HbA1c below 6 percent. There was a trend for higher risks of stroke and deaths due to heart failure, while myocardial infarction was not affected. Both, combined cardiovascular events and mortality were increased at higher levels of HbA1c, which was mainly explained by the impact of HbA1c on sudden death.

When enrolling into the 4D Study, patients had an average history of known diabetes 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% for the highest proportion of deaths in the 4D Study, while only 11% of deaths were attributed to MI and adjudicated coronary heart disease[3]. Similar information was reported from the United States Renal Data System which showed that 27% of deaths in dialysis patients had been classified as cardiac arrest or cardiac arrhythmia, and only 8% as deaths due to acute MI and atherosclerotic heart disease[2].

A number of different causes may account for sudden death in dialysis patients, including micro- and macrovascular disease, sympathetic overactivity, structural heart disease, cardiac fibrosis, and electrolyte and volume shifts due to the hemodialysis procedure [9, 13, 14]. 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[15], and impaired myocardial vasodilator function[16], which contribute to cardiac microvessel disease and structural heart disease[17]. It has been reported that hyperglycemia induced excess generations of

highly reactive free radicals causing oxidative stress, and inflammatory cytokines[17, 18]. 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 (AGEs), which are known to excert and amplify oxidative stress and vice versa can also be a consequence of oxidative stress. These AGE toxins are profibrotic and directly involved in the pathogenesis of the inflammatory reponse syndrome and vascular complications.

Myocardial fibrosis has mechanical and electrical sequelae which impact on cardiovascular prognosis[19]. It reduces the ventricular compliance and promotes arrhythmia by causing local delay in the spread of the action potential[20, 21]. In an animal model of mild diabetes, researchers observed an enhanced susceptibility to ventricular arrhythmias, with increased electrophysiological sensitivity to catecholamines and nonhomogenous collagen accumulation affecting local conduction[22]. Studies in diabetic patients found regional cardiac denervation and sympathetic overactivity, potentially resulting in life-threatening myocardial electrical instability[23, 24]. In line with these findings, HbA1c was reported to be a predictor of spontaneous ventricular arrhythmias in diabetic patients with an implantable-cardioverter-defibrillator[25].

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[26, 27]. In chronic kidney disease patients the literature is not unequivocal. While several studies reported lower survival rates for diabetic patients with poor glycemic control [28-30], another study in 24,875 maintenance hemodialysis patients from Fresenius dialysis clinics in the United States did not indicate any association between HbA1c and 1 year survival[31]. Even though 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[32]. Data from 23,618 patients in DaVita outpatient clinics over 3 years showed in unadjusted survival analyses paradoxically lower death hazard ratios with higher HbA1c values. However, after adjusting 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[33].

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 if tight glycemic control might even increase the risk of death querying the role of glycemic control to be a risk factor[34, 35]. In this context, it is of special interest to distinguish between micro- and macrovascular complications. 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 discussed to result from both macro- and microvascular components in diabetic patients [36]. These observations are in line with results from the ADVANCE study, which showed that the beneficial effect of intensive glycemic control was mainly achieved by the reduction of microvascular complications, while macrovascular events alone could not significantly be reduced[35]. However, macrovascular events with predominantly MI account for the majority of deaths in diabetic patients from the general population[37], possibly partly explaining 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 high proportions of sudden cardiac deaths, and atherosclerotic deaths playing a minor role only [2, 3]. Whereas the effect of tight glycemic control on macrovascular complications is still under debate, its effect on microvascular complications has repeatedly been shown[27, 34, 35, 38, 39]. 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 post-hoc analysis within a selected cohort of German patients with T2DM on hemodialysis. Therefore, the relationship between HbA1c and risk may not be generalisable to other patient populations. HbA1c measurement in patients on hemodialysis treatment might have been compromised by reduced red blood cell lifespan[40] and the widespread use of erythropoietin increasing the proportion of reticulocytes and younger red blood cells with less time for glycosylation to occur[41]. This may have lead to an underestimation of HbA1c levels, but due to its general nature it is unlikely to have influenced our results,

which were based on comparisons within the same study population. The specific outcomes, among which sudden cardiac death, and their association with HbA1c to be analyzed was the main **strength** of this study. In this context, the long-term follow-up, adequate sample size and high incidence of pre-specified and centrally adjudicated endpoints are further to be mentioned.
In conclusion, glycemic control as represented by the level of HbA1c was strongly associated with sudden cardiac death in hemodialysed type 2 diabetic patients. While myocardial infarction was not affected, the risks of the combined primary endpoint and mortality significantly increased at higher levels of HbA1c, and were mainly explained 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.

Acknowledgements:

We thank all investigators and study nurses who participated in the 4D Study; without their collaboration this article would not have been written. Special thanks goes to the laboratory staffs at the Universities of Freiburg, Heidelberg and Würzburg, especially Simone Dietz and Katja Blouin. We also thank the clinical epidemiologists Dr. Friedo Dekker for the discussions and Dr. Diana Grootendorst for the advise and critical proof-reading of the manuscript.

FUNDING SOURCES: C. Drechsler thanks the European Renal Association - European Dialysis and Transplant Association, and the Deutsche Forschungsgemeinschaft (DR 804/1-1) for the support with a research fellowship. We furthermore thank the Interdisziplinäres Zentrum für klinische Forschung of the University of Würzburg for the support with a research grant.

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