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ARTICLE

Diabetes, glycaemic control and mortality risk in patients on haemodialysis: the Japan Dialysis Outcomes and Practice Pattern Study

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Abstract
Aims/hypothesis There are few data on the target level of glycaemic control among patients with diabetes on haemodialysis. We investigated the impact of glycaemic control on mortality risk among diabetic patients on haemodialysis.
Subjects and methods Data were analysed from the Dialysis Outcomes Practice Pattern Study (DOPPS) for randomly selected patients on haemodialysis in Japan. The diagnosis of diabetes at baseline and information on clinical events during follow-up were abstracted from the medical records. A Cox proportional hazards model was used to evaluate the association between presence or absence of diabetes, glycaemic control (HbA_{1c} quintiles) and mortality risk.
Results Data from 1,569 patients with and 3,342 patients without diabetes on haemodialysis were analysed. Among patients on haemodialysis, those with diabetes had a higher mortality risk than those without (multivariable hazard ratio 1.37, 95% CI 1.08–1.74). Compared with those in the bottom quintile of HbA_{1c} level, the multivariable-adjusted hazard ratio for mortality was not increased in the bottom second to fourth quintiles of HbA_{1c} (HbA_{1c} 5.0–5.5% to 6.2–7.2%), but was significantly increased to 2.36 (95% CI 1.02–5.47) in the fifth quintile ($HbA_{1c} \geq 7.3\%$). The effect of poor glycaemic control did not statistically correlate with baseline mortality risk ($p=0.27$).
Conclusions/interpretation Among dialysis patients, poorer glycaemic control in those with diabetes was associated with higher mortality risk. This suggests a strong effect of poor glycaemic control above an HbA_{1c} level of about 7.3% on mortality risk, and that this effect does not appear to be influenced by baseline comorbidity status.

Keywords Diabetes · Glycaemic control · Haemodialysis

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Abbreviations
DOPPS Dialysis Outcomes and Practice Pattern Study
ESRD end-stage renal disease

Introduction

Type 2 diabetes mellitus is one of the most prevalent chronic diseases in many countries. More than 20 million people have diabetes in the USA, more than double the number 20 years ago, and 90–95% of cases are type 2 diabetes [1, 2]. Furthermore, about 7.4 million people have diabetes in Japan [3]. Diabetes imposes a substantial burden, and is the leading cause of end-stage renal failure [4]. The economic cost of diabetes is estimated to be as much as US$100 billion per year in Japan and is the same in the USA [5, 6].

Several large randomised controlled trials, including the Diabetes Control and Complications Trial, the Kumamoto Study and the UK Prospective Diabetes Study (UKPDS), have proved the efficacy of intensive glycaemic control in preventing the development and progression of diabetic microangiopathy, comprising retinopathy, nephropathy and neuropathy [7–9]. The importance of glycaemic control in patients is maintained even after the development of diabetic complications.

It was reported that a high HbA_{1c} level was linearly associated with a high mortality risk in a cohort of 4,662 diabetic men irrespective of haemodialysis status [10]. Among haemodialysis patients, those with diabetes have higher mortality than those without it [11]; and among patients with diabetes on haemodialysis, HbA_{1c}>7.5% is associated with higher mortality risk [12]. Although these studies have suggested an association between diabetes and mortality, it remains unclear whether patients with diabetes and 'good' glycaemic control have higher mortality risk than those without diabetes, or whether the relationship between higher HbA_{1c} level and risk is linear or subject to a threshold effect.

The objective of this study was to test two hypotheses in the Dialysis Outcomes and Practice Pattern Study (DOPPS). First, we examined whether diabetic haemodialysis patients with good glycaemic control had an elevated mortality risk compared with non-diabetic haemodialysis patients. Second, we evaluated whether a threshold exists in the relationship between HbA_{1c} level and mortality risk among diabetic haemodialysis patients.

Subjects and methods

Study population DOPPS is an international prospective observational study of haemodialysis practice patterns and associated outcomes. Originally, this study aimed to clarify which dialysis practices most contributed to improved mortality rates, hospitalisation rates, health-related quality of life and vascular access outcomes, after adjusting for the effects of comorbid disease and demographic variables. DOPPS phase I was conducted from 1997 to 2001 in France, Germany, Italy, Japan, Spain, the UK and the USA; DOPPS phase II was conducted from 2002 to 2004, with the added participation of Australia, New Zealand, Belgium, Canada and Sweden. The phase III study is ongoing in the USA, five countries in Europe (France, Germany, Italy, Spain and the UK, known collectively as the Euro-DOPPS countries) and Japan. Details of the subjects and methods have been reported elsewhere [13]. Briefly, the dialysis facilities included in DOPPS are a nationally representative sample. A stratified random sample of chronic haemodialysis facilities was selected to ensure variation in practice patterns and outcomes. The sampling frame consisted of a random subsample of a national list of haemodialysis facilities. At the start of the project, the study coordinator in each participating facility conducted a census of current in-centre haemodialysis patients older than 17 years, included basic information such as age, race, sex and the cause of end-stage renal disease (ESRD). Within each facility, the census listing was then used to select a random sample of 20–40 patients, varying according to the size of the facility. Institutional review boards approved the study in each country or facility as required. Informed patient consent was obtained in accordance with the requirements of each country, review board and dialysis centre. Data collection was performed in a fashion that maintained patient anonymity at the coordinating centre. Because HbA_{1c} data from the other countries were not available, we included only Japanese cohort data from phases I and II.

Data collection Information, including diabetes status and glycaemic control, was abstracted from patient charts by a study coordinator in each facility. The study coordinator also completed a medical questionnaire which addressed a variety of areas. These included the primary cause of ESRD, comorbidities including diabetes, duration of dialysis, age, sex, BMI, and laboratory data including HbA_{1c} and haemoglobin levels at baseline. In addition, the study coordinator completed an interval summary approximately every 4 months for each sampled patient, which included the occurrence of hospitalisation, outpatient events, death, and the primary cause of death. This summary was used to calculate the time to event data.

Definition of diabetes A patient was considered diabetic if the primary cause of ESRD was diabetes, diabetes mellitus was a comorbidity, oral hypoglycaemic agents or insulin therapy were prescribed, or HbA_{1c} was ≥6.5% at baseline.

Diabetes was considered not present if the primary cause of ESRD was not diabetes, diabetes was not present as a comorbidity, and HbA_{1c} testing had not been done. HbA_{1c} in one subject was 19.9%, a ratio usually unachievable in patients on haemodialysis, and this subject was therefore treated as lacking HbA_{1c} data. A total of 3,342 non-diabetic and 1,569 diabetic patients were included in the present analysis.

Statistical analysis We used direct standardisation to compare categorical variables adjusted for age, and the generalised linear model procedure to compare age-adjusted continuous measurements. Survival rate was analysed as the time from entry into the study to patient death. Patients were censored from contributing additional survival data following a switch in treatment to peritoneal dialysis or transplantation, following change to a non-DOPPS haemodialysis facility, or at the time of the last round of data collection for a given facility, whichever came first. Cumulative survival rate curves for patients with and without diabetes were constructed using the Kaplan–Meier method and survival rates were compared using the log-rank test. The magnitude of associations between diabetes, HbA_{1c} level and mortality risk was estimated using the Cox proportional hazards model stratified by study phase. Statistical models were constructed with consideration of facility clustering.

First, we compared mortality risk between diabetic and non-diabetic patients. We next evaluated the mortality risk of patients with different HbA_{1c} levels (quintiles) compared with non-diabetic patients. For this analysis, we excluded patients whose primary cause of ESRD was diabetes or who had diabetes as a comorbidity but did not undergo HbA_{1c} testing at baseline. Two multivariable regression models were constructed. The first (model 1) controlled for variables considered to be potential confounders of the association between diabetes and mortality, namely age (continuous), BMI (continuous), duration of dialysis (quartiles) and haemoglobin levels (continuous). The second model (model 2) controlled for all variables in model 1, as well as smoking status, type of treatment for diabetes mellitus, history of hyperlipidaemia, history of hypertension, years from initiation of haemodialysis (quartiles), and presence of comorbidities (cerebrovascular disease, coronary artery disease, congestive heart failure, other cardiovascular disease, peripheral vascular disease, lung disease, cancer, gastrointestinal disease). Age- and multivariable-adjusted hazard ratios and the corresponding 95% CIs were tested using both models. The proportional hazards assumption was tested by calculating Schoenfeld residuals [14, 15]; if the assumption is met, the null hypothesis of a zero slope in a generalised linear regression of the scaled Schoenfeld residuals as a function of time is held.

Next, to evaluate the hypothesis that the effect of poor glycaemic control on mortality may vary depending on baseline mortality risk, we evaluated the joint association between glycaemic control ($HbA_{1c}<7.3\%$, $HbA_{1c}\geq7.3\%$) and comorbidities (no known comorbidity, at least one comorbidity other than diabetes). Likelihood ratio tests were used to test statistical interactions between study glycaemic control and comorbidity by comparing the −2 log(likelihood) between two nested models, one with only the main effects, and the other with the main effects and interaction terms.

To evaluate the association between glycaemic control and the cause of death, we categorised the cause of death into four groups: cardiovascular disease, stroke, infectious disease, and other. Cardiovascular disease comprised acute myocardial infarction, pericarditis, ischaemic heart disease, cardiomyopathy, arrhythmia, cardiac arrest, valvular disease of the heart, pulmonary congestion, congenital heart disease and pulmonary embolism. Infectious disease comprises sepsis, peritonitis, pneumonia (bacterial, fungal), viral infection, tuberculosis and HIV infection. The Cochran–Armitage exact trend test was used to evaluate the association between HbA_{1c} quintile and cause of death category.

All statistical analyses were performed with SAS version 8.2 (SAS, Inc., Cary, NC, USA) and Intercooled Stata 8.2 (Stata Corporation, College Station, TX, USA).

Results

Data from 1,569 patients with and 3,342 patients without diabetes on haemodialysis were analysed (mean age, 59 years; range, 18–95 years). Baseline characteristics of all patients according to the presence or absence of diabetes and HbA_{1c} quintile are shown in Table 1. Patients without diabetes had a smaller BMI and more years since the initiation of haemodialysis than those with diabetes, as well as less coronary artery disease, cerebrovascular disease, congestive heart failure and peripheral vascular disease.

During the 7,792 person-years of follow-up (median follow-up period, 1.9 years), 407 deaths were recorded. Figure 1 shows that the cumulative survival rate was significantly higher in non-diabetic patients than in patients with diabetes ($p<0.001$). The age-adjusted hazard ratio of diabetes for mortality was 1.40 (95% CI, 1.12–1.61) (Table 2). Further adjustments for sex and BMI intensified the risk value. Risk was slightly attenuated but remained significant (hazard ratio 1.37, 95% CI 1.08–1.74) in a multivariable model adjusted for age, sex, haemoglobin, smoking status, type of treatment for diabetes mellitus, hyperlipidaemia, hypertension, cerebrovascular disease, coronary artery disease, congestive heart failure, other cardiac disease, peripheral artery disease, lung disease,

Table 1 Baseline characteristics of participants according to diabetes and glycaemic control quintiles

Characteristic	No diabetes (n=3,340)	Diabetes (HbA_{1c} quintile)					
		Quintile 1 (n=110)	Quintile 2 (n=126)	Quintile 3 (n=115)	Quintile 4 (n=127)	Quintile 5 (n=114)	Missing HbA_{1c} (n=979)
HbA_{1c} (%)							
Mean	–	4.5	5.2	5.9	6.7	8.2	–
Median	–	4.7	5.2	5.9	6.7	7.9	–
Range	–	3.3–4.9	5.0–5.5	5.6–6.1	6.2–7.2	7.3–13.1	–
Age (years)[a]	58.9±13.5	64.7±11.8	63.9±11.7	64.2±9.0	63.8±10.9	61.7±10.8	63.3±10.7
Sex (% male)	59.0	68.2	72.4	73.3	60.6	62.3	69.2
BMI (kg/m^2)[b]	20.2±0.05	21.2±0.30	21.2±0.28	22.0±0.29	21.4±0.27	21.5±0.29	21.0±0.10
Haemoglobin (g/l)[b]	97±0.3	95±1.4	94±1.3	97±1.3	98±1.3	98±1.4	95±0.5
Hyperlipidaemia (%)	5.3	14.5	15.0	16.4	21.3	21.1	5.3
Hypertension (%)	56.7	90.0	81.1	72.7	70.0	78.1	74.0
Type of treatment for diabetes (%)							
None	100	85.5	74	69.8	63.0	60.5	84.0
Oral hypoglycaemic agent only	0	10.0	18.9	20.7	17.3	21.1	9.1
Insulin	0	4.5	7.1	9.5	19.7	18.4	6.9
Duration of dialysis (%)							
Quartile 1 (0–0.89 years)	18.8	47	47.2	40.6	38.6	36.1	18.8
Quartile 2 (0.90–3.88 years)	22.2	30.3	26.0	28.4	37.0	25.2	32.6
Quartile 3 (3.89–9.12 years)	26.1	12.7	21.3	25.0	18.9	26.1	23.9
Quartile 4 (9.13–34.6 years)	32.9	10.0	5.5	6.0	5.5	12.6	8.6
Comorbidities (%)							
Cerebrovascular disease	10.5	18.2	20.5	18.1	14.2	14.9	24.1
Coronary artery disease	18.5	35.5	29.1	27.6	33.1	35.1	26.6
Congestive heart failure	10.5	28.2	23.6	28.4	26.0	30.7	18.6
Other cardiovascular disease	25.4	32.7	29.1	28.4	29.1	34.2	26.1
Peripheral vascular disease	7.2	9.1	14.2	20.7	26.0	26.3	21.5
Lung disease	1.7	0.0	1.6	2.6	1.6	1.8	1.9
Cancer	6.0	2.7	7.1	6.9	6.3	6.1	6.5
Gastrointestinal disease	4.0	5.5	8.7	8.6	6.3	4.4	4.4

[a] Mean±SD
[b] Mean±SE

cancer, gastrointestinal disease, neurological disease, and years from the initiation of haemodialysis quartiles.

We next evaluated the effect of different HbA_{1c} levels on mortality risk. Compared with those in the bottom quintile of HbA_{1c}, the age-adjusted hazard ratio for mortality did not increase in the second (1.23, 95% CI 0.51–2.93) to fourth (1.07, 95% CI 0.42–2.70) quintiles, but did increase to 2.38 (95% CI, 1.08–5.25) in the fifth quintile (Table 3).

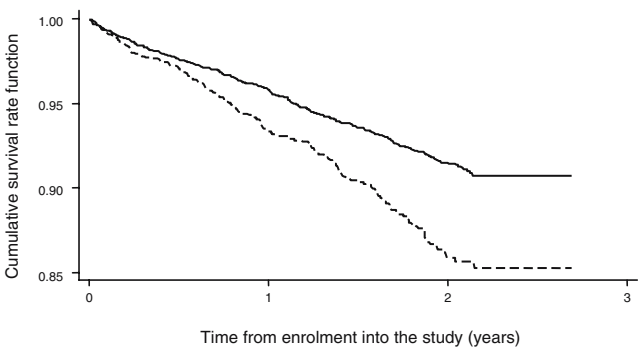

Fig. 1 Kaplan–Meier estimates for survival rates among patients on haemodialysis with and without diabetes. Estimates for patients without diabetes are represented as a *solid line* and those for patients with diabetes as a *dotted line*

Table 2 Diabetes and mortality risk in patients on haemodialysis, accounting for facility clustering, stratified by phase of DOPPS

	Hazard ratio for mortality (95% CI)		
	Age-adjusted	Model 1[a]	Model 2[b]
No diabetes	1	1	1
Diabetes	1.40 (1.12–1.61)	1.43 (1.15–1.78)	1.37 (1.08–1.74)

[a] Adjusted for age, sex, haemoglobin and BMI
[b] Adjusted for age, sex, haemoglobin, smoking status, type of treatment for diabetes mellitus, hyperlipidaemia, hypertension, cerebrovascular disease, coronary artery disease, congestive heart failure, other cardiac disease, peripheral artery disease, lung disease, cancer, gastrointestinal disease and duration of dialysis

Table 3 Glycaemic control and mortality risk

	No diabetes (n=3,340)	Diabetes (HbA_{1c} quintiles)						p value for trend across HbA_{1c} quintiles
		Quintile 1 (n=110)	Quintile 2 (n=126)	Quintile 3 (n=115)	Quintile 4 (n=127)	Quintile 5 (n=114)	Missing HbA_{1c} (n=979)	
HbA_{1c} (%)	–	3.3–4.9	5.0–5.5	5.6–6.1	6.2–7.2	7.3–19.9	–	
Person-years	5,520	142	168	159	185	161	1,457	
Number of deaths	245	8	11	8	10	17	108	
Hazard ratio (95% CI)								
Age-adjusted	1.20 (0.60–2.40)	1	1.23 (0.51–2.93)	0.98 (0.43–2.21)	1.07 (0.42–2.70)	2.38 (1.08–5.25)	1.80 (0.89–3.65)	0.0136
Model 1[a]	1.07 (0.55–2.10)	1	1.28 (0.54–3.04)	1.20 (0.54–2.69)	1.30 (0.51–3.29)	2.55 (1.17–5.56)	1.85 (1.66–2.05)	0.032
Model 2[b]	1.04 (0.53–2.05)	1	1.20 (0.52–2.73)	0.80 (0.35–1.84)	1.20 (0.46–3.12)	2.36 (1.02–5.47)	1.57 (0.79–3.13)	0.1110

[a] Adjusted for age, sex, haemoglobin and BMI

[b] Adjusted for age, sex haemoglobin, smoking status, type of treatment for diabetes mellitus, hyperlipidaemia, hypertension, cerebrovascular disease, coronary artery disease, congestive heart failure, other cardiac disease, peripheral artery disease, lung disease, cancer, gastrointestinal disease and duration of dialysis

This association was slightly attenuated in multivariable model 2, which was adjusted for age, sex, haemoglobin, smoking status, type of treatment for diabetes mellitus, hyperlipidaemia, hypertension, cerebrovascular disease, coronary artery disease, congestive heart failure, other cardiac disease, peripheral artery disease, lung disease, cancer, gastrointestinal disease and duration of dialysis, but mortality risk in the fifth quintile remained significantly higher than in non-diabetic patients. There was a significant trend between HbA_{1c} quintile and mortality risk in the age-adjusted model (p for trend=0.0136), but this trend diminished in multivariable models (p for trend=0.1110). The multivariate adjusted hazard ratio for haemodialysis patients without diabetes was similar to that in the reference group. The multivariate-adjusted hazard ratio for 979 patients with diabetes who did not undergo HbA_{1c} testing at baseline was 1.57 (95% CI 0.79–3.13).

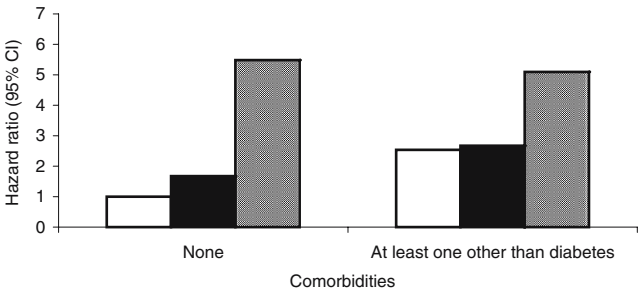

Fig. 2 Joint effect of diabetes and comorbidities on mortality risk. Hazard ratios for death according to diabetes status, including HbA_{1c} levels and presence or absence of comorbidities other than diabetes based on a multivariable model, are shown. The multivariable model was adjusted for age (continuous), sex, BMI (continuous), haemoglobin level (continuous), and years after initiation of haemodialysis in quartiles. *Open bar*, no diabetes (at least one comorbidity: 95% CI 1.83–3.52); *black bar*, diabetes, HbA_{1c} <7.3% (no comorbidities: 95%CI 0.72–3.9; at least one comorbidity other than diabetes: 95% CI 1.63–4.39); *grey bar*, diabetes, HbA_{1c} ≥7.3% (no comorbidities: 95% CI 2.5–12.0; at least one comorbidity other than diabetes: 95% CI 2.75–9.43)

We conducted stratified analyses to examine whether the effect of glycaemic control on mortality varied depending on comorbidities other than diabetes (Fig. 2). Among patients without comorbidities, compared with those without diabetes, the hazard ratio for mortality of patients with diabetes and HbA_{1c} equal to or greater than 7.3% was 4.90 (95% CI, 2.30–10.42). Mortality seemed more strongly exacerbated by poor glycaemic control in these patients than in those without comorbidities. The effect of glycaemic control, however, did not vary significantly depending on the presence or absence of comorbidities (p=0.27, 2 df, χ^2= 2.59). The proportional hazard assumption was met in all models.

The associations between cause of death and HbA_{1c} quintile are shown in Table 4. A high HbA_{1c} level appeared to be associated with a high frequency of cardiovascular diseases, albeit with borderline significance (p=0.0559). We did not observe a significant association between HbA_{1c} level and stroke (p=0.7901) or infectious disease (p=0.3658).

Discussion

The DOPPS data have revealed that haemodialysis patients with diabetes have a higher mortality risk than those without diabetes. Among previous studies of diabetes, glycaemic control and mortality, the systematic review by Johnson et al. of the effect of diabetes on survival rates in patients on

Table 4 Causes of death of patients with diabetes and HbA_{1c} testing at baseline during follow-up

HbA_{1c} quintiles (Range of HbA_{1c}, %)	Quintile 1 (3.3–4.9) (n=110)	Quintile 2 (5.0–5.5) (n=126)	Quintile 3 (5.6–6.1) (n=115)	Quintile 4 (6.2–7.2) (n=127)	Quintile 5 (7.3–13.1) (n=115)	p value for trend[a]
Cause of death						
Cardiovascular disease	2 (1.8%)	4 (3.2%)	4 (3.5%)	5 (3.9%)	8 (7.0%)	0.0559
Stroke	2 (1.8%)	2 (1.6%)	0 (0.0%)	1 (0.8%)	2 (1.7%)	0.7901
Infectious disease	3 (2.7%)	2 (1.6%)	2 (1.7%)	2 (1.6%)	1 (0.9%)	0.3658
Other	1 (0.9%)	3 (2.4%)	2 (1.7%)	2 (1.6%)	6 (5.2%)	0.0988
Total	8 (7.3%)	11 (8.7%)	8 (7.0%)	10 (7.9%)	17 (14.8%)	0.1011

Percentages are expressed per total number of subjects in each quintile
[a] Cochrane–Armitage exact trend test

dialysis showed that the pooled relative mortality risk associated with the presence of diabetes was 1.91 compared with patients without diabetes; however, they did not consider the effect of glycaemic control [11]. Although our multivariable adjusted hazard ratio of 1.37 is smaller than their pooled estimate, our diabetes sample had relatively good glycaemic control, and only 20% of patients with diabetes had HbA_{1c} levels ≥7.3% (fifth quintile). Although actual glycaemic control was not described in the original articles cited in their review [16–26], the different glycaemic control may explain the different estimates of mortality risk.

Morioka et al. evaluated the clinical significance of glycaemic control in diabetic ESRD patients on haemodialysis, and revealed that, among patients with diabetes, those with poor glycaemic control (HbA_{1c}≥7.5%) had a higher mortality risk than those with good control (HbA_{1c}< 7.5%) [12]. To date, however, two issues on glycaemic control and mortality have not been resolved, namely whether patients with diabetes and good glycaemic control have a higher mortality risk than those without diabetes, and whether there is any threshold of glycaemic control associated with a higher mortality risk among diabetes patients on haemodialysis. Our present results answer both these questions.

First, among dialysis patients, those with diabetes but good glycaemic control had similar mortality risk to those without diabetes. Second, there did appear to be a threshold of glycaemic control in association with mortality risk. Specifically, only the patients with the highest quintile of HbA_{1c} level had significantly higher mortality risk than those without diabetes. This result suggests that HbA_{1c} ratios less than 7.3% are an adequate goal for glycaemic control in patients with diabetes on haemodialysis. This finding is consistent with the results of a previous report [12].

Why did well-controlled diabetes itself not increase the mortality risk in patients with diabetes on haemodialysis? Many patients with ESRD on haemodialysis have comorbidities, including coronary artery disease, peripheral artery disease, other cardiac disease or cerebrovascular disease, and thus have an already high mortality risk. Thus, the influence of glycaemic control on mortality may be attenuated by the presence of diabetes compared with patients who do not have comorbidities other than diabetes. We therefore hypothesised that the effect of glycaemic control on mortality may vary depending on baseline mortality risk, and thus conducted a joint analysis between glycaemic control and the presence of comorbidity. Results suggested that the effect of glycaemic control may be attenuated in patients with at least one comorbidity other than diabetes; however, no statistically significant interaction between these factors was seen, indicating that the degree of importance of glycaemic control was not clearly influenced by baseline mortality risk. Furthermore, our relatively small sample size might have limited the power to detect a significant result. Further evaluation of the relationship between glycaemic control at baseline and mortality risk is therefore required. The hazard ratio with comorbidities is no higher than—in fact it appears to be less than—that without comorbidities for patients with HbA_{1c} levels >7.3%. The small sample size of patients with a poor glycaemic index may explain the very wide confidence intervals of the hazard ratios, and thus might have resulted in inaccurate point estimates.

A good correlation between HbA_{1c} and blood glucose levels in patients without ESRD was documented in the Diabetes Control and Complications Trial [7, 27]. Because this study did not include patients with ESRD and only very few with advanced renal disease, there may be concern that the HbA_{1c} levels do not correlate with blood glucose levels. In particular, HbA_{1c} might underestimate actual glycaemic levels in patients with ESRD; namely, measured HbA_{1c} is lower than that expected from measured blood glucose levels. Two studies have investigated the association between HbA_{1c} and blood glucose level. Joy et al. evaluated the association between several glycaemic control tests (HbA_{1c}, total glycated haemoglobin, fructosamine and glycated plasma proteins) and blood glucose levels, and found that despite anaemia and a shortened erythrocyte lifespan, HbA_{1c} and total glycated haemoglobin correlated most strongly with actually measured blood glucose levels,

whereas fructosamine and glycated plasma protein correlated poorly [28]. These results may support the use of HbA_{1c} for monitoring glycaemic control in patients on haemodialysis. Morgan et al. suggested that haemodialysis patients had lower than expected HbA_{1c} levels relative to ambient glucose concentrations [29], but as this conclusion was drawn from linear regression analysis from only three measurements in three patients, the reliability of this result is questionable.

There are several possible reasons for the poorer prognosis in those with worse glycaemic control. Several studies have shown an association between stringent glycaemic control and a lowered risk of developing cardiovascular disease and death [30–32], but this finding has not been consistent. In our study, patients in the poorer glycaemic control group tended to have a higher frequency of cardiovascular death, although without statistical significance, probably owing to the relatively small sample size.

Our results should be interpreted with caution. The International Diabetes Federation and the Japan Diabetes Society both recommend maintaining HbA_{1c} at <6.5% [33], whereas the American Diabetes Association recommends <7% [34]. Although our value of 7.3% is slightly higher than the target levels mentioned above, hypoglycaemia is a common medical problem in patients with haemodialysis [35]. Consideration should be given to the balance required between the benefit of lowering blood glucose and the risk of hypoglycaemia in patients with diabetes on haemodialysis.

There are several limitations in our study. Because the data we analysed were observational, the findings might be explained by bias and confounding. If present, however, these would be reduced by the prospective design for data collection and adjustment for many covariates that may be confounders in the association of diabetes, glycaemic control and mortality. Our sample was limited to a Japanese population, which may limit extrapolation to other ethnic groups. Against this, the mortality risk ratio for diabetes mellitus showed little variation among seven countries, of which Japan was one [36, 37]. We therefore doubt that the population we studied would limit the generalisability of our results. Baseline data on HbA_{1c} were often missing, which was unavoidable, given that the main aim of the DOPPS was to measure dialysis practice variation. Nevertheless, this lack of baseline data might not have distorted the representativeness of the original sample.

In conclusion, among dialysis patients, poorer glycaemic control in those with diabetes was associated with a higher mortality risk than in patients without diabetes. The effect of poor glycaemic control on the mortality risk increased sharply above the HbA_{1c} level of about 7.3%, and its effect on mortality was not influenced by the baseline mortality risk.

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Duality of interest There was no duality of interest for any of the authors.

References

1. Centers for Disease Control and Prevention (2004) Number of persons with diagnosed diabetes, United States, 1980–2002. Available from http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm, accessed 22 December 2004
2. Kawakami F, Ito M, Matsuda Y, Hayashi I, Ohtsuki K (2004) The effects of cholesterol-3-sulfate (CH-3S) on the phosphorylation of human C3a (hC3a) in vitro and on the ability of hC3a to induce vascular permeability in rats. Biol Pharm Bull 27:282–287
3. Harris MI, Klein R, Welborn TA, Knuiman MW (1992) Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. Diabetes Care 15:815–819
4. American Diabetes Association (2004) Type 2 diabetes complications. Available from http://www.diabetes.org/type-2-diabetes/complications.jsp, accessed 22 December 2004
5. Ettaro L, Songer TJ, Zhang P, Engelgau MM (2004) Cost-of-illness studies in diabetes mellitus. PharmacoEconomics 22:149–164
6. Central Social Insurance Medical Council (2003) Medical economics survey [in Japanese]. Available from http://www.mhlw.go.jp/shingi/2005/01/s0126-8.html, accessed 24 February 2007
7. The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329:977–986
8. Ohkubo Y, Kishikawa H, Araki E et al (1995) Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 28:103–117
9. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352:837–853
10. Khaw KT, Wareham N, Luben R et al (2001) Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). Br Med J 322:15–18
11. Johnson JG, Gore SM, Firth J (1999) The effect of age, diabetes, and other comorbidity on the survival of patients on dialysis: a systematic quantitative overview of the literature. Nephrol Dial Transplant 14:2156–2164
12. Morioka T, Emoto M, Tabata T et al (2001) Glycemic control is a predictor of survival for diabetic patients on hemodialysis. Diabetes Care 24:909–913
13. Young EW, Goodkin WA, Mapes DL et al (2000) The Dialysis Outcomes and Practice Patterns Study (DOPPS): an international hemodialysis study. Kidney Int 57(Suppl 74):S74–S81
14. Grambsch PM, Therneau TM (1994) Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 81:515–526
15. Therneau T (1995) Splus 3.3 guide to statistical and mathematical analysis. Mathsoft, Seattle
16. Khan IH, Campbell MK, Cantarovich D et al (1996) Survival on renal replacement therapy in Europe: is there a 'centre effect'? Nephrol Dial Transplant 11:300–307

17. McClellan WM, Anson C, Birkeli K, Tuttle E (1991) Functional status and quality of life: predictors of early mortality among patients entering treatment for end stage renal disease. J Clin Epidemiol 44:83–89
18. McClellan WM, Flanders WD, Gutman RA (1992) Variable mortality rates among dialysis treatment centers. Ann Intern Med 117:332–336
19. Nicolucci A, Cubasso D, Labbrozzi D et al (1992) Effect of coexistent diseases on survival of patients undergoing dialysis. ASAIO J 38:M291–M295
20. Salem MM, Bower J (1996) Hypertension in the hemodialysis population: any relation to one-year survival? Am J Kidney Dis 28:737–740
21. Iseki K, Nishime K, Uehara H, Osawa A, Fukiyama K (1994) Effect of renal diseases and comorbid conditions on survival in chronic dialysis patients. Nephron 68:80–86
22. Lupo A, Tarchini R, Carcarini G et al (1994) Long-term outcome in continuous ambulatory peritoneal dialysis: a 10-year-survey by the Italian Cooperative Peritoneal Dialysis Study Group. Am J Kidney Dis 24:826–837
23. Mailloux LU, Bellucci AG, Napolitano B, Mossey T, Wilkes BM, Bluestone PA (1994) Survival estimates for 683 patients starting dialysis from 1970 through 1989: identification of risk factors for survival. Clin Nephrol 42:127–135
24. Iseki K, Osawa A, Fukiyama K (1993) Evidence for increased cancer deaths in chronic dialysis patients. Am J Kidney Dis 22:308–313
25. Gentil MA, Carriazo A, Pavon MI et al. (1991) Comparison of survival in continuous ambulatory peritoneal dialysis and hospital haemodialysis: a multicentric study. Nephrol Dial Transplant 6:444–451
26. Chazan JA, Lew NL, Lowrie EG (1991) Increased serum aluminum. An independent risk factor for mortality in patients undergoing long-term hemodialysis. Arch Intern Med 151: 319–322
27. Goldstein DE, Wiedmeyer HM, Little RR, Vargas V, Nair SS, Reid J (1997) Relationship between glycohemoglobin (GHB) and mean blood glucose (MBG) in the Diabetes Control and Complications Trial (DCCT). Diabetes Care 46:8A
28. Joy MS, Cefalu WT, Hogan SL, Nachman PH (2002) Long-term glycemic control measurements in diabetic patients receiving hemodialysis. Am J Kidney Dis 39:297–307
29. Morgan L, Marenah CB, Jeffcoate WJ, Morgan AG (1996) Glycated proteins as indices of glycaemic control in diabetic patients with chronic renal failure. Diabet Med 13:514–519
30. Nathan DM, Lachin J, Cleary P et al (2003) Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med 348:2294–2303
31. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O (2003) Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 348:383–393
32. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M (2003) Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 290:486–494
33. IDF Clinical Guidelines Task Force (2006) Global Guideline for Type 2 Diabetes: recommendations for standard, comprehensive, and minimal care. Diabet Med 23:579–593
34. American Diabetes Association (2006) Standards of medical care in diabetes—2006. Diabetes Care 29(Suppl 1):S4–S42
35. Bilous RW (2004) End-stage renal failure and management of diabetes. Diabet Med 21(Suppl 1):12–14
36. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB (1998) Prediction of coronary heart disease using risk factor categories. Circulation 97:1837–1847
37. Menotti A, Blackburn H, Seccareccia F et al. (1997) The relation of chronic diseases to all-cause mortality risk—the seven countries study. Ann Med 29:135–141