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Original Article

ORIGINAL ARTICLE

Recurrent cardiovascular events in patients with type 2 diabetes and haemodialysis: analysis from the 4D Study

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ABSTRACT

Background. In the 'Die Deutsche Diabetes Dialyse Studie' (4D Study), treatment of patients with type 2 diabetes mellitus (T2DM) on haemodialysis (HD) with atorvastatin compared with placebo had no significant effect on the first composite primary major adverse cardiovascular event (MACE) endpoint of death from cardiac causes, fatal stroke, non-fatal myocardial infarction or non-fatal stroke. In this study we analysed first and recurrent events in 1255 patients from the 4D Study.

Methods. We conducted an event history analysis to investigate the effects of previous clinical events on the risk of different endpoints in the total patient group and after stratification by randomization group.

Results. During a median follow-up of 4 years, a total of 548 MACEs occurred, with 469 first and 79 recurrent events. The most frequent event was sudden cardiac death, followed by death due to infection/sepsis. Of the 548 total MACEs, 260 occurred in the atorvastatin group and 288 in the placebo group [hazard ratio 0.91 (95% confidence interval 0.76–1.07), $P = .266$]. Interestingly, analyses of the baseline hazard functions for first and recurrent events as a function of time after randomization demonstrated that the risks of the composite primary endpoint continually increased in the placebo group with increasing time in the study, whereas the risk in the atorvastatin group remained constant after ≈1.5 years.

Conclusion. This recurrent and total event analysis from the 4D Study underscores the high risk of sudden cardiac death and death due to infection/sepsis in patients with T2DM receiving HD and raises the hypothesis that atorvastatin may stabilize cardiovascular risk only after 1–2 years in this high-risk population.

LAY SUMMARY

We analysed first and recurrent events in 1255 patients with type 2 diabetes mellitus (T2DM) on haemodialysis (HD) from the 'Die Deutsche Diabetes Dialyse Studie', in which treatment with atorvastatin compared with placebo had no

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significant effect on the first composite primary major adverse cardiovascular event. Our data suggest that sudden cardiac death and death caused by infection/sepsis were the most frequent events in patients with T2DM receiving HD. In addition, our analysis on baseline hazard functions for first and recurrent primary endpoint events raises the hypothesis that atorvastatin may stabilize cardiovascular risk in this population after 1.5 years.

Keywords: atorvastatin, 4D Study, haemodialysis, outcomes, type 2 diabetes mellitus

INTRODUCTION

The 'Die Deutsche Diabetes Dialyse Studie' (4D Study) was a randomized, placebo-controlled trial in patients with type 2 diabetes mellitus (T2DM) receiving maintenance haemodialysis (HD) treatment that investigated the effect of atorvastatin 20 mg/day on major adverse cardiovascular events (MACEs). In this study, atorvastatin, compared with placebo, had no significant effect on the composite primary endpoint of death from cardiac causes, fatal stroke, non-fatal myocardial infarction (MI) or non-fatal stroke, thus suggesting that initiation of lipid-lowering therapy in patients with T2DM and end-stage kidney disease (ESKD) may be too late to translate into a decrease in cardiovascular (CV) events [1]. Similar results have also been obtained for rosuvastatin versus placebo in A Study to Evaluate the Use of Rosuvastatin in participants on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [2]. As in most cardiovascular outcome trials (CVOTs), the 4D Study used time-to-first-event analyses. These analyses are suboptimal for chronic diseases such as T2DM or chronic kidney disease (CKD), because relevant information on recurrent events is ignored and the effect of a given intervention on the total morbidity burden is not captured [3].

Patients with T2DM receiving HD have a notably high risk of developing CV events, and epidemiological and clinical data have shown that sudden cardiac death is the most frequent CV event in patients receiving HD [4, 5]. Nonetheless, the effects of previous non-fatal clinical events, such as MI or stroke, on the risk of subsequent events in patients with T2DM receiving HD are unclear but may be important to help guide clinical decision making. In addition, the effects of previous clinical events on the efficacy of lipid-lowering statin treatment in decreasing the risk of subsequent events are unexplored.

Therefore, we conducted an event history analysis of the 4D Study data to investigate the effects of previous clinical events (CV events and hospitalizations) on the risk of different endpoints in the total patient group and after stratification by randomization group (atorvastatin versus placebo).

MATERIALS AND METHODS

The 4D Study was a multicentre, randomized, double-blind, prospective study enrolling 1255 participants with T2DM receiving maintenance HD at 178 centres who were randomly assigned to receive 20 mg of atorvastatin or matching placebo daily. The study rationale and design were as previously described [6]. In the placebo group, one patient was lost to follow-up and 150 patients discontinued treatment before the end of the study. In the atorvastatin group, no patients were lost to follow-up and 142 patients discontinued treatment before the end of the study. The primary endpoint was a composite of death from cardiac causes, non-fatal MI and stroke. Secondary endpoints included death from all causes and all cardiac and cerebrovascular events. Endpoint definitions and endpoint assessment procedures have been described in detail elsewhere [7]. As previously reported, atorvastatin had no statistically significant effect on the composite MACE endpoint of CV death, non-fatal MI and non-fatal stroke {relative risk [RR] 0.92 [95% confidence interval (CI) 0.77–1.10], $P = .37$} [1].

Statistical methods

We applied the Prentice, Williams and Petersen (PWP) counting process model, an extension of the Cox proportional hazards model for multiple events [8], which allows for recurrent events in the same patient and accounts for a change in risk during follow-up, on the basis of the occurrence of previous clinical events (hospitalizations and non-fatal CV events). Furthermore, the model assumes an event-specific baseline hazard and estimates cause-specific hazard ratios (HRs) by treating competing events as censored observations. For each endpoint, we fitted several prognostic models for three different patient populations (all patients, patients in the atorvastatin group and patients in the placebo group), adjusting for different sets of covariates. First, we fitted a univariate model including only the clinical event of interest (e.g. non-fatal MI) as a time-varying covariate. Second, we used a multivariate model additionally including any other previous clinical event as a time-varying covariate (e.g. non-fatal stroke or hospitalization). The third model additionally adjusted for age, sex, duration of diabetes, time on HD, systolic blood pressure, body mass index (BMI), haemoglobin A1c, erythropoietin use and a history of coronary heart disease at baseline. For the endpoints of CV and non-CV death, we additionally fitted a competing risk regression model estimating subdistribution HRs to address potential selection bias due to the covariate-dependent competing risk process [9]. All prognostic models for the total population were fitted with stratification by treatment group (atorvastatin versus placebo). In addition, we fitted an efficacy model aimed to estimate the effect of atorvastatin, including first and recurrent events, by including the respective randomization group as a predictor variable adjusted for sex and baseline coronary heart disease status. In all recurrent event models, the correlation among repeated events in the same participant was addressed by adjusting the variance–covariance matrix by using a grouped jack-knife estimator [10]. For sensitivity analysis, we implemented a landmark time-to-event analysis approach including only patients that reached the landmark of 12 months of follow-up. The landmark analysis starts the follow-up at 12 months and weights patients inversely to the probability to reach the landmark. Probability weights were estimated by fitting a logistic regression model to the full trial study population that identified the prognostic factors sex, BMI, haemoglobin, phosphate, leucocyte count, creatinine, time of HD, duration of diabetes, New York Heart Association score, coronary heart disease, peripheral vascular disease, cardiac valve disorder,

Table 1: Observed recurrent events, classified by order of event occurrence (N = 1255 patients with T2DM receiving HD).

	Event order[a]								
Type of event	1	2	3	4	5	6	7	Total	Rate[b]
Sudden cardiac death	119	28	12	1	0	0	0	160	45.0
Death caused by infection/sepsis	92	24	8	3	0	0	1	128	36.0
PTCA, non-fatal	56	31	7	4	1	0	0	99	27.9
Silent MI	73	17	5	2	1	0	0	98	27.6
Non-cardiac/cerebrovascular death, other causes	66	12	4	1	0	1	0	84	23.6
Non-fatal MI	54	11	3	0	0	0	0	68	19.1
TIA/PRIND	51	9	4	0	0	0	0	64	18.0
Non-fatal ischaemic stroke	45	10	2	1	0	0	0	58	16.3
Fatal MI	42	10	4	0	0	0	0	56	15.8
Non-cardiac/cerebrovascular death, unknown cause	38	11	1	1	0	0	0	51	14.4
ACVB, non-fatal	35	10	0	1	2	1	0	49	13.8
Death caused by CHF	35	6	0	0	0	0	0	41	11.5
Death caused by cancer	32	3	1	0	0	0	0	36	10.1
Fatal ischaemic stroke	15	8	1	0	1	0	0	25	7.0
Non-fatal stroke of unclear type	5	3	1	0	0	0	0	9	2.5
Fatal haemorrhagic stroke	6	2	0	0	0	0	0	8	2.3
Death caused by pulmonary embolism	6	2	0	0	0	0	0	8	2.3
Fatal stroke of unclear type	5	2	0	0	0	0	0	7	2.0
Death during/after ACVB	3	1	1	0	1	0	0	6	1.7
Death from other coronary causes	5	1	0	0	0	0	0	6	1.7
Non-fatal haemorrhagic stroke	4	0	1	0	0	0	0	5	1.4
Death during/after PTCA	1	0	0	0	0	0	0	1	0.3
Other intervention, caused by CHD, non-fatal	1	0	0	0	0	0	0	1	0.3
Total	789	201	55	14	6	2	1	1068	300.6

ACVB: aortocoronary venous bypass; CHD: congenital heart disease; CHF: congestive heart failure.
[a]Order of occurrence of the event among all recurrent events in a patient.
[b]Rate per year per 1000 patients.

angina pectoris and the use of angiotensin-converting enzyme inhibitors as predictors to survive the 12 months. All *P*-values are two-sided. Statistical analyses were conducted in Stata version 16 (StataCorp, College Station, TX, USA).

RESULTS

Effects of previous non-fatal events on the risk of subsequent events

The baseline characteristics of patients in the placebo and atorvastatin group are shown in Supplementary Table S1. During a median follow-up of 4 years, a total of 548 MACEs (death from cardiac causes, fatal stroke, non-fatal MI or non-fatal stoke) occurred among the 1255 trial participants, with 469 first events and 79 recurrent events, thus reflecting a 17% increase in events with respect to first events. Of the assessed outcomes, the increase was 11% in MIs (fatal or non-fatal, also including silent MI; 200 first events only, 222 total events), 9% in stroke (fatal and non-fatal; 103 first, 112 total) and 24% in total hospitalizations (1107 first, 4603 total).

The overall event rate during the trial, including an overview of the sequence of events, is shown in Table 1. The most frequent event in this high-risk population of patients with T2DM receiving HD was sudden cardiac death, which was followed by death caused by infection/sepsis, with annual event rates of 4.5% and 3.6%, respectively.

Baseline characteristics of patients with one or two or more events were not statistically different, as shown in Supplementary Table S2.

Effect of previous clinical events on endpoint occurrence overall and according to study treatment

In the placebo group, a previous non-fatal MI increased the risk of a subsequent primary endpoint event, with an HR of 2.26 (95% CI 0.79–6.5) even after multivariate adjustment and a similar HR [2.50 (95% CI 0.78–7.99)] in atorvastatin-treated patients. In addition, after a first non-fatal MI, the risk of a subsequent MI (fatal or non-fatal, including silent MI) increased by 2.44-fold (95% CI 0.30–19.84) in the placebo group but not in the atorvastatin group [HR 0.79 (95% CI 0.09–6.88)]. The HRs of CV death after a first non-fatal MI were 1.75 (95% CI 0.95–3.22) in the placebo group and 0.93 (95% CI 0.37–2.34) in the atorvastatin group. Interestingly, in both groups, previous hospitalization had the strongest effect on CV death [placebo: HR 3.27 (95% CI 2.02–5.29); atorvastatin: HR 2.01 (95% CI 1.06–3.82)], non CV-death [placebo: HR 6.76 (95% CI 3.68–12.42); atorvastatin: HR 3.81 (95% CI 2.08–6.97)] and overall mortality [placebo: HR 4.65 (95% CI 3.14–6.90); atorvastatin: HR 3.04 (95% CI 1.99–4.63)] (Table 2).

Efficacy of atorvastatin including recurrent events

Of the 548 total combined primary endpoint events, 260 occurred in the atorvastatin group, whereas 288 occurred in the placebo group, thus resulting in an annual incidence rate of 14.7% in the statin group and 16.2% in the placebo group and a crude incidence rate ratio of 0.91 (95% CI 0.76–1.07, $P = .266$). After adjustment for age and all other predictive baseline covariates, the HR was 0.86 (95% CI 0.73–1.03, $P = .103$). Separate evaluation of endpoint components showed a 20% decrease in cardiac death [HR 0.80 (95% CI 0.63–1.02)] and a 16% decrease in non-fatal MI

Table 2: Effects of previous critical clinical events on endpoint occurrence overall and according to study treatment.

	M0: Univariate			M1: Multivariate			M2: Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
(A) Primary endpoint (death from cardiac causes, fatal stroke, non-fatal MI or non-fatal stroke)									
Total population (1255 patients, 548 events including recurrent events +17% compared with 469 first events only)									
Previous clinical event									
Hospitalisation (≥1: 4603 events)	**2.14**	**1.61–2.83**	**<0.001**	**2.14**	**1.61–2.83**	**<0001**	**2.24**	**1.71–2.95**	**<0.001**
Non-fatal MI (≥1: 166 events)	**1.86**	**1.09–3.18**	**0.023**	**2.49**	**1.25–4.9**	**0.010**	**2.61**	**1.23–5.55**	**0.013**
Non-fatal stroke (≥1: 72 events)	1.13	0.57–2.25	0.730	1.84	0.79–4.28	0.156	1.78	0.71–4.48	0.220
Atorvastatin group (619 patients, 260 events including recurrent events +15% compared with 226 first events only)									
Previous clinical event									
Hospitalisation (≥1: 2287 events)	**1.63**	**1.08–2.46**	**0.021**	**1.64**	**1.09–2.48**	**0.018**	**1.67**	**1.08–2.58**	**0.021**
Non-fatal MI (≥1: 91 events)	**2.67**	**1.27–5.64**	**0.010**	**3.41**	**1.24–9.35**	**0.017**	**2.50**	**0.78–7.99**	**0.123**
Non-fatal stroke (≥1: 30 events)	0.79	0.35–1.77	0.562	1.77	0.65–4.88	0.264	2.12	0.64–6.95	0.640
Placebo group (636 patients, 288 events including recurrent events +19% compared with 243 first events only)									
Previous clinical event									
Hospitalisation (≥1: 2316 events)	**2.65**	**1.82–3.86**	**<0.001**	**2.63**	**1.79–3.86**	**<0.001**	**2.88**	**2.01–4.12**	**<0.001**
Non-fatal MI (≥1: 75 events)	1.38	0.67–2.85	0.377	1.82	0.74–4.50	0.193	2.26	0.79–6.50	0.130
Non-fatal stroke (≥1: 42 events)	1.55	0.54–4.45	0.412	1.64	0.48–5.61	0.430	1.82	0.41–8.19	0.432
(B) MI (fatal or non-fatal)									
Total population (1255 patients, 222 events including recurrent events +11% compared with 200 first events only)									
Previous clinical event									
Non-fatal MI (≥1: 166 events)	**2.07**	**0.96–4.46**	**0.063**	**1.65**	**0.74–3.65**	**0.013**	1.48	0.54–4.06	0.443
Non-fatal stroke (≥1: 72 events)	1.75	0.72–4.26	0.216	1.51	0.63–3.64	0.360	1.18	0.44–3.17	0.744
Atorvastatin group (619 patients, 98 events including recurrent events +9% compared with 90 first events only)									
Previous clinical event									
Non-fatal MI (≥1: 91 events)	**1.01**	**0.14–7.20**	**0.999**	**0.92**	**0.11–7.63**	**0.936**	0.79	0.09–6.88	0.835
Non-fatal stroke (≥1: 30 events)	0.95	0.22–4.01	0.944	0.96	0.23–4.06	0.956	0.94	0.12–7.51	0.955
Placebo group (636 patients, 124 events including recurrent events +13% compared with 110 first events only)									
Previous clinical event									
Non-fatal MI (≥1: 75 events)	2.56	0.30–22.10	0.392	**1.49**	**0.21–10.38**	**0.686**	**2.44**	**0.30–19.84**	**0.405**
Non-fatal stroke (≥1: 42 events)	2.13	0.63–7.17	0.224	2.74	0.57–13.09	0.207	1.96	0.50–7.75	0.335

Table 2: Continued

(C) Stroke (fatal or non-fatal) Total population (1255 patients, 112 events including recurrent events +9% compared with 103 first events only)									
Previous clinical event									
Non-fatal MI (≥1: 166 events)	**3.54**	**1.21–10.37**	**0.021**	3.39	1.21–9.50	1.210	**2.99**	**1.32–4.5**	**0.004**
Atorvastatin group (619 patients, 64 events including recurrent events +8% compared with 59 first events only)									
Previous clinical event									
Non-fatal MI (≥1: 91 events)	**34.4**	**3.68–321.60**	**0.002**	**29.39**	**1.01–4.73**	**0.047**	**22.09**	**1.11–439.71**	**0.043**
Placebo group (636 patients, 48 events including recurrent events +9% compared with 44 first events only)									
Previous clinical event									
Non-fatal MI (≥1: 75 events)	1.41	0.49–4.04	0.526	**2.69**	**1.10–6.55**	**0.030**	2.26	0.15–3.92	0.738
(D) Death from CV causes Total population (1255 patients, 310 events)									
Previous clinical event									
Hospitalisation (≥1: 4603 events)	**2.55**	**1.76–3.70**	**<0.001**	**2.54**	**1.77–3.65**	**<0.001**	**2.70**	**1.87–3.89**	**<0.001**
Non-fatal MI (≥1: 166 events)	1.58	0.96–2.60	0.069	1.51	0.97–2.35	0.065	1.42	0.88–2.28	0.152
Non-fatal stroke (≥1: 72 events)	0.97	0.40–2.36	0.950	1.07	0.50–2.32	0.859	0.83	0.35–1.98	0.682
Atorvastatin group (619 patients, 148 events)									
Previous clinical event									
Hospitalisation (≥1: 2287 events)	**2.02**	**1.12–3.62**	**0.019**	**1.99**	**1.11–3.56**	**0.020**	**2.01**	**1.06–3.82**	**0.032**
Non-fatal MI (≥1: 91 events)	1.35	0.67–2.72	0.400	1.44	0.77–2.67	0.254	0.93	0.37–2.34	0.879
Non-fatal stroke (≥1: 30 events)	0.71	0.27–1.92	0.510	0.83	0.32–2.12	0.696	0.94	0.30–2.92	0.914
Placebo group (636 patients, 162 events)									
Previous clinical event									
Hospitalisation (≥1: 2316 events)	**3.10**	**1.93–4.98**	**<0.001**	**2.99**	**1.87–4.77**	**<0.001**	**3.27**	**2.02–5.29**	**<0.001**
Non-fatal MI (≥1: 75 events)	**1.88**	**1.01–3.47**	**0.045**	1.63	0.91–2.92	0.104	1.75	0.95–3.22	0.073
Non-fatal stroke (≥1: 42 events)	2.00	0.49–8.13	0.334	1.39	0.30–6.46	0.676	1.00	0.18–5.56	0.996
(E) Death from non-CV causes Total population (1255 patients, 307 events)									
Previous clinical event									
Hospitalisation (≥1: 4603 events)	**5.64**	**3.40–9.36**	**<0.001**	**5.41**	**3.30–8.87**	**<0.001**	**5.44**	**3.44–8.62**	**<0.001**
Non-fatal MI (≥1: 166 events)	0.98	0.40–2.40	0.962	0.94	0.55–1.62	0.831	1.00	0.61–1.64	0.999
Non-fatal stroke (≥1: 72 events)	**3.44**	**1.95–6.08**	**<0.001**	**2.27**	**1.19–4.32**	**0.012**	**2.24**	**1.29–3.86**	**0.004**

Table 2: Continued

Atorvastatin group (619 patients, 149 events)									
Previous clinical event									
Hospitalisation (≥1: 2287 events)	**4.52**	**2.54–8.06**	**<0.001**	**4.25**	**2.42–7.48**	**<0.001**	**3.81**	**2.08–6.97**	**<0.001**
Non-fatal MI (≥1: 91 events)	1.68	0.69–4.09	0.249	0.91	0.42–1.94	0.798	1.27	0.60–2.69	0.524
Non-fatal stroke (≥1: 30 events)	**7.53**	**3.86–14.70**	**<0.001**	**5.06**	**2.49–10.26**	**<0.001**	**5.69**	**2.76–11.76**	**<0.001**
Placebo group (636 patients, 158 events)									
Previous clinical event									
Hospitalisation (≥1: 2316 events)	**6.73**	**3.32–13.63**	**<0.001**	**6.64**	**3.28–13.46**	**<0.001**	**6.76**	**3.68–12.42**	**<0.001**
Non-fatal MI (≥1: 75 events)	0.74	0.22–2.54	0.635	1.00	0.47–2.13	0.999	0.70	0.37–1.34	0.285
Non-fatal stroke (≥1: 42 events)	2.03	0.97–4.22	0.060	1.22	0.51–2.89	0.651	0.52	0.22–1.20	0.124
(F) Death from all causes									
Total population (1255 patients, 617 events)									
Previous clinical event									
Hospitalisation (≥1: 4603 events)	**3.72**	**2.78–4.97**	**<0.001**	**3.71**	**2.79–4.94**	**<0.001**	**3.82**	**2.85–5.12**	**<0.001**
Non-fatal MI (≥1: 166 events)	1.22	0.79–1.89	0.363	1.09	0.77–1.57	0.607	1.03	0.73–1.44	0.863
Non-fatal stroke (≥1: 72 events)	**2.14**	**1.13–4.04**	**0.019**	**2.10**	**1.24–3.57**	**0.006**	**1.84**	**1.04–3.24**	**0.036**
Atorvastatin group (619 patients, 297 events)									
Previous clinical event									
Hospitalisation (≥1: 2287 events)	**2.90**	**1.88–4.47**	**<0.001**	**3.08**	**2.03–4.68**	**<0.001**	**3.04**	**1.99–4.63**	**<0.001**
Non-fatal MI (≥1: 91 events)	1.38	0.83–2.28	0.217	1.04	0.63–1.72	0.870	0.90	0.58–1.39	0.631
Non-fatal stroke (≥1: 30 events)	1.78	0.70–4.52	0.225	2.37	1.20–4.65	0.013	2.50	1.29–4.86	0.007
Placebo group (636 patients, 320 events)									
Previous clinical event									
Hospitalisation (≥1: 2316 events)	**4.53**	**3.02–6.80**	**<0.001**	**4.41**	**2.94–6.62**	**<0.001**	**4.65**	**3.14–6.90**	**<0.001**
Non-fatal MI (≥1: 75 events)	1.12	0.57–2.20	0.742	1.14	0.67–1.92	0.629	1.07	0.62–1.83	0.805
Non-fatal stroke (≥1: 42 events)	**2.74**	**1.24–6.04**	**0.013**	**1.72**	**0.68–4.35**	**0.253**	**1.37**	**0.54–3.47**	**0.505**

M0: Univariate model adjusted for clustering per centre by robust variance estimation. M1: multivariate model adjusted for the effects of other previous critical clinical events (non-fatal MI, non-fatal stroke and hospitalization). M2: M1 + adjusted for age, sex, duration of diabetes, time receiving HD, systolic blood pressure, BMI, haemoglobin A1c, erythropoietin use and a history of coronary artery disease at baseline.

Table 3: Efficacy estimates of atorvastatin, obtained in first event and multiple event analysis.

	Time to first event				Multiple events			
Endpoint	Events, *n*	HR [a]	95% CI	*P*-value	Events, *n*	HR	95% CI	*P*-value
Combined primary endpoint	469	0.92	0.77–1.10	0.370	548	0.86	0.73–1.03	0.112
Death from cardiac causes[b]	270	0.81	0.64–1.03	0.080				
Non-fatal MI	149	0.88	0.64–1.21	0.420	166	0.84	0.62–1.14	0.258
Fatal stroke	40	2.03	1.05–3.93	0.040	40	1.78	0.91–3.47	0.092
Non-fatal stroke	65	1.04	0.64–1.69	0.890	72	1.03	0.63–1.71	0.881
All cardiac events[c]	451	0.82	0.68–0.90	0.040	585	0.80	0.66–0.96	0.020
All cerebrovascular events[d]	149	1.12	0.81–1.55	0.490	176	1.13	0.84–1.52	0.424
Stroke	103	1.33	0.90–1.97	0.150	112	1.33	0.90–1.97	0.151
Death from all causes	617	0.93	0.79–1.08	0.330				
Death from other causes than CV	307	0.95	0.76–1.18	0.620				

[a]Hazard ratios adjusted for sex and history of coronary artery disease at baseline.
[b]Death from cardiac causes: fatal MI, sudden cardiac death and death by congestive heart failure.
[c]All cardiac events: death from cardiac causes, non-fatal MI, silent MI, aortocoronary venous bypass, PTCA or other non-fatal intervention caused by coronary artery disease.
[d]All cerebrovascular events: fatal or non-fatal stroke, non-cardiac/cerebrovascular death, other causes or TIA/PRIND.

[HR 0.84 (95% CI 0.62–1.14)], but an absence of a benefit in stroke [fatal stroke: HR 1.78 (95% CI 0.91–3.47); non-fatal stroke: HR 1.03 (95% CI 0.63–1.71)]. Additional analyses revealed a 20% decrease in all cardiac events [death from cardiac causes, non-fatal MI, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft and other interventions to treat coronary artery disease] in the atorvastatin group [HR 0.80 (95% CI 0.66–0.96)] but a slightly increased rate of cerebrovascular events [stroke, transient ischaemic attack (TIA)/prolonged reversible ischaemic neurological deficit (PRIND): HR 1.13 (95% CI 0.84–1.52)]. The HR for total mortality was 0.89 (95% CI 0.76–1.04) (Table 3, Supplementary Table S3). A detailed event analysis of patients in the two study groups is shown in Supplementary Table S3. The respective Kaplan–Meier curves are shown in Supplementary Fig. S1.

Next, we analysed the baseline hazard functions for first and recurrent events as a function of time after randomization. In the placebo group, the risk of the composite primary endpoint continually increased with increasing time in the study, whereas the risk in the atorvastatin group remained constant after ≈1.5 years (Fig. 1a). Similar hazard profiles were observed for the endpoints of MI (Fig. 1b), thus suggesting that atorvastatin treatment appeared to stabilize the increase in risk of cardiac endpoints during the study over time. In contrast, the HR for fatal stroke was higher in the intervention group, and this difference remained constant during the entire follow-up period (Fig. 1c). Finally, both groups exhibited a substantially increasing CV mortality rate with increasing study duration, with a slightly smaller increase in the intervention group (Fig 1d). The landmark analysis corroborated our findings that the associations were similar to the original analysis (Supplementary Table S4).

DISCUSSION

In this exploratory total event analysis of the 4D Study, we found that sudden cardiac death and death caused by infection/sepsis were the most frequent events in this high-risk population of patients with T2DM receiving HD. In addition, our analysis of baseline hazard functions for first and recurrent primary endpoint events raises the hypothesis that atorvastatin may stabilize CV risk in this population after ≈1.5 years, mainly by exhibiting a positive effect on MI.

The recurrent event data from our study provide important information on the total morbidity burden in patients with T2DM receiving HD. During the median follow-up period of 4 years, 49% of all patients in the study died, thus underscoring the extremely high mortality risk in this population. Our data from 1255 very well-characterized patients with carefully adjudicated events allowed for detailed analysis of the causes of death as well as the sequence of events over time. Sudden cardiac death (with an annual event rate of 4.5%) and death caused by infection/sepsis (with an annual event rate of 3.6%) were the major causes of death. More importantly, these events were by far the most frequent of all events in this study. In our study population, sudden cardiac death and death by infection/sepsis most often occurred as the first event but had a much lower incidence as the second or third event after an initial non-fatal event. These data are consistent with previous results from registries and retrospective analyses on the one hand, showing high overall mortality risk in this population [4, 5, 11], but on the other hand, demonstrating different sequences of events between patients with T2DM receiving HD and patients with T2DM without CKD. Recurrent event data from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients trial in patients with T2DM with CV disease but preserved kidney function [estimated glomerular filtration rate (eGFR) 74 ± 21 ml/min/1.73 m^2 at baseline] showed a comparable first event rate for MI and CV death in the placebo group (5.3% and 5.9%, respectively) and a much lower rate for non-CV death (2.4%) as a first event [12]. Similar analyses have been published from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial [13]. Our observation that sudden cardiac death was the most frequent first and overall event in the 4D Study suggests that patients with T2DM receiving HD exhibit a substantially different event risk profile from that in patients with T2DM with preserved eGFR. This difference is probably due to characteristic pathophysiological alterations in the heart in ESKD, such as fibrosis [14] and hypertrophy [15], as well as volume and sudden electrolyte shifts [16], all of which are known to increase the risk of sudden cardiac death.

In addition, our recurrent events analysis in the placebo group demonstrates that T2DM patients on HD after a first non-fatal MI exhibit a 2.26-fold or 2.44-fold increased risk to develop a primary endpoint event or a subsequent MI (fatal, non-fatal),

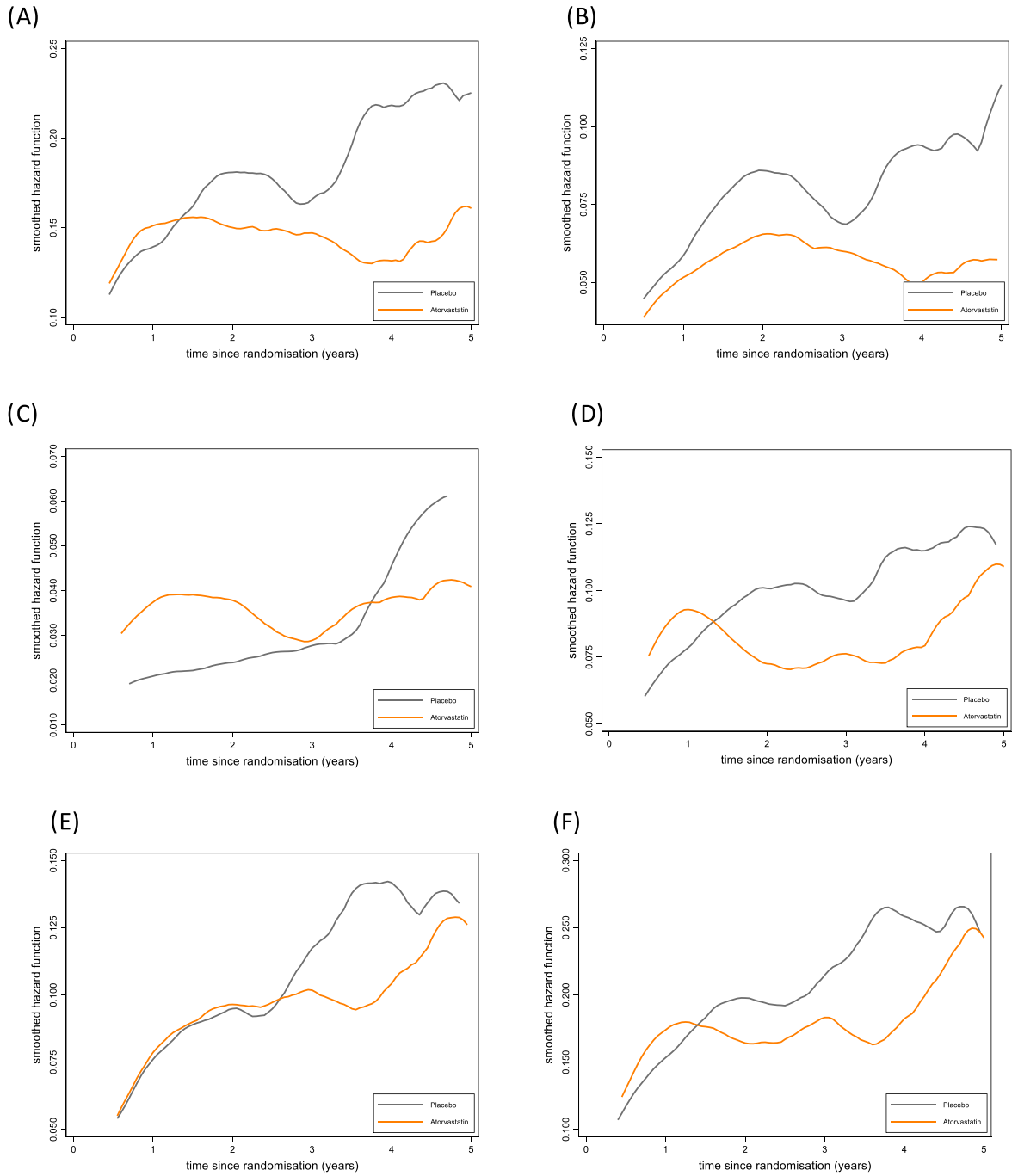

Figure 1: Baseline hazard functions as a function of time after randomization (atorvastatin group versus placebo group, including recurrent events). **(A)** Primary endpoint (death from cardiac causes, fatal stroke, non-fatal MI or non-fatal stroke), **(B)** MI (fatal or non-fatal), **(C)** stroke (fatal or non-fatal), **(D)** death from CV causes, **(E)** death from non-CV causes, **(F)** death from all causes. Smoothed baseline hazard estimates as a function of time since randomization. Estimates >5 years are not shown because of inconsistency due to very few events.

respectively. However, the risk of death did not increase after a non-fatal MI, thus potentially suggesting that patients might have received more stringent therapy overall after they experienced a non-fatal MI. Interestingly, in this high-risk population of patients, our data suggest that previous hospitalization might be the strongest predictor of a subsequent primary endpoint event, CV death, non-CV death or all-cause mortality, with the highest HR of 6.76 for the risk of non-CV death. Given the wide confidence intervals, the data need to be interpreted with caution. Still, the results underscore that many other clinical events beyond CV complications are important drivers of the high overall mortality in this population, thus suggesting that after these patients are hospitalized, they have a substantially elevated risk of dying over the next years.

In the initial time-to-first-event analysis in the 4D Study, atorvastatin treatment had no significant effect on the combined

time-to-first-event primary endpoint. Analysis of all events in this study did not change this overall result and showed that atorvastatin did not decrease the risk of subsequent CV events after an initial non-fatal event. Nonetheless, atorvastatin decreased the combined secondary exploratory endpoint of all cardiac events, thus suggesting that statin treatment might have at least moderately mitigated the increased risk of cardiac endpoints during the study, but this effect was not as potent as that in patients not receiving HD. In addition, baseline hazard functions for first and recurrent primary endpoint events raise the hypothesis that atorvastatin may stabilize CV risk in this population after ≈1.5 years. Various large CVOTs have shown that low-density lipoprotein (LDL) cholesterol lowering with statins as well as other drugs, such as proprotein convertase subtilisin/kexin type 9 inhibitors, decreases the cardiovascular endpoints in high-risk patients with or without T2DM through beneficial effects on arteriosclerosis-related events such as MI [17–19]. In all these studies, patients with ESKD receiving kidney replacement therapy were excluded. In the 4D Study, despite an effective lowering of LDL cholesterol by 42% from baseline, atorvastatin had no significant effect on the time-to-first-event combined endpoint or on recurrent and total events. These results suggest that the lipid-lowering intervention in this population of patients with T2DM receiving HD may have come too late and that the increased CV risk in these patients could no longer be diminished through a therapeutic strategy focusing mainly on modulating arteriosclerosis-related events. In addition, the high rate of death from causes other than CV or cerebrovascular disease and the finding that previous hospitalizations are the best risk indicator of overall mortality indicate the frailty of HD patients with T2DM.

Limitations

Our analysis has certain limitations. The 4D Study started in 1998 and, at that time, state-of-the-art therapy in patients with diabetes was different and did not include novel agents such as sodium–glucose co-transporter-2 inhibitors or glucagon-like peptide-1 receptor agonists. In addition, LDL targets are different nowadays, and the results both of the 4D Study itself as well as the data from our current analysis may be look different if the study were conducted today. The statistical methods employed have certain limitations: as in all post hoc analyses, we cannot rely on *P*-values because clinical and statistical significance do not converge. Some hypotheses tests might not have enough power because the study has not been primarily defined to answer this research questions. Thus the results may only be seen as hypothesis generating and should not change current recommendations for the treatment of HD patients with T2DM. Finally, changes in co-medication after an event were not available for our analysis. However, given that the prognosis of patients with T2DM and HD is still reduced today, and given that no therapy over the last 2 decades has been shown to reduce CV risk in this population, our data provide novel information on the overall burden of disease in these patients.

In summary, our analysis of recurrent and total events from the 4D Study underscores the high risk of sudden cardiac death and death due to infection/sepsis in patients with T2DM receiving HD and raises the hypothesis that atorvastatin may stabilize CV risk only after 1–2 years in this high-risk population.

SUPPLEMENTARY DATA

Supplementary data is available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

N.M. designed the project and wrote the first draft and revised the manuscript. C.W., W.M. and V.K. were investigators of the 4D trial, revised the concept and the manuscript. J.J. designed the project with N.M. and revised the manuscript. B.G. performed statistical analyses.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract format.

(See related article by Ebert and Bárány. Lifelong statins for long life in dialysis patients? *Clin Kidney J* (2023) 16: 1541–1542.)

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