High cardiovascular event rates occur within the first weeks of starting hemodialysis

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Early mortality is high in hemodialysis (HD) patients, but little is known about early cardiovascular event (CVE) rates after HD initiation. To study this we analyzed data in the AROii cohort of incident HD patients from over 300 European Fresenius Medical Care dialysis centers. Weekly rates of a composite of CVEs during the first year and monthly rates of the composite and its constituents (coronary artery, cerebrovascular, peripheral arterial, congestive heart failure, and sudden cardiac death) during the first 2 years after HD initiation were assessed. Of 6308 patients that started dialysis within 7 days, 1449 patients experienced 2405 CVEs over the next 2 years. The first-year CVE rate (30.2/100 person-years; 95% CI, 28.7–31.7) greatly exceeded the second-year rate (19.4/100; 95% CI, 18.1–20.8). Composite CVEs were highest during the first week with increased risk compared with the second year, persisting until the fifth month. Except for sudden cardiac death, temporal patterns of rates for all CVE categories were very similar, with highest rates during the first month and a high-risk period extending to 4 months. Higher or lower cumulative weekly dialysis dose, lower blood flow, and lower net ultrafiltration during dialysis were associated with CVE during the high-risk period, but not during the post high-risk period. Thus, the incidence of CVE in the first weeks after HD initiation is much higher than during subsequent periods which raises concerns that HD initiation may trigger CVEs.

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In patients with chronic kidney disease (CKD) the first months on hemodialysis (HD) have been identified as a high-risk period for patient survival.[1] In both the US[2–7] and Europe,[7–9] increased mortality during the first 3 months after dialysis initiation, compared with subsequent periods, has been observed. The underlying reasons remain poorly understood. Early dialysis withdrawal may contribute to early mortality,[3] but withdrawal practice varies significantly across countries and overall accounts for a comparatively small proportion of early death.[7] Among other causes of death, up to 40% have been attributed to cardiovascular (CV) disease[8,9] and a large study found the greatest difference between mortality rates during the first 3 months and during the remainder of the first year on dialysis for CV-related deaths.[3] Thus, study of CV events (CVE) after dialysis initiation should lead to a better understanding of the causes of early mortality, risk prediction, and preventive strategies in high-risk patients. However, there is a paucity of data on CVE rates following HD initiation. In particular, it is not known whether the time to event varies for specific CVE categories, whether CVE risk factors vary for different CVE categories, and whether CVE risk factors differ for early and subsequent periods on dialysis.

The clinical circumstances of dialysis initiation vary, making analysis of the early time period after starting dialysis challenging. Although many patients will initiate HD in an outpatient setting, others will have their first dialysis during a hospitalization period and will be subsequently referred to dialysis centers after variable time periods. Thus, important clinical events may easily be missed in registries of chronic HD patients. In fact, because of these circumstances and additional administrative reasons, many large registries do not capture clinical data on the first months on HD.[10] Smaller studies, on the other hand, may have been of insufficient size

to provide reliable rate estimates for different CVEs,[11,12] although they have been important in characterizing early mortality after dialysis initiation.

Utilizing data collected prospectively as part of the ARO (Analyzing data, Recognizing excellence, and Optimizing outcomes) CKD research initiative,[13] we studied the occurrence of CVE after dialysis initiation in a large cohort of incident HD patients at over 300 Fresenius Medical Care dialysis centres in Europe (FME; 'AROii'). Inclusion criteria for the current study were carefully chosen, and different scenarios for patients initiating HD within and outside the FME network were considered to reliably capture early events.

RESULTS
Study population
The AROii cohort includes 11,244 incident patients presenting to FME centers in 14 European countries and Turkey. Patients most frequently initiated HD on the day of study enrollment ($n = 3974$) or within a week of this date ($n = 2270$), whereas ~40% ($n = 4882$) initiated HD at an earlier time point and a small proportion at later time points ($n = 118$; see Supplementary Figure S1 online). For the purpose of the current study we chose to exclude patients with a dialysis vintage of $\geqslant 7$ days ($n = 4569$) and patients who did not initiate dialysis within 365 days of admission to FME ($n = 21$). Furthermore, we excluded sequentially patients with no dialysis data ($n = 484$) or with a history of kidney transplantation ($n = 83$), thus resulting in a study cohort of 6308 patients. Within this study cohort 4005 patients (63%) initiated dialysis within FME facilities and the remainder initiated dialysis elsewhere.

Patient characteristics
A total of 2405 CVEs were reported in 1449 patients (23% of the study cohort) within 2 years after initiation of dialysis. The characteristics of the study cohort stratified by the occurrence of at least one CVE in the 2-year study period are described in Table 1. Patients who experienced events in the first 2 years after dialysis initiation tended to be older and were more frequently male. They more often had vascular or diabetic causes for their CKD, and this pattern was repeated in their pre-dialysis clinical history, with a greater prevalence of the constituent CVE and diabetes observed. Also the percentage of former smokers was higher in those experiencing a CVE. Conversely, no geographical differences were apparent, and patients were similar with regard to social relationship and current smoking status.

The characteristics of patients starting dialysis in FME facilities and those starting dialysis elsewhere are shown in Supplementary Table S1 online. With the exception of geography (a higher proportion of FME facilities in Eastern Europe are hospital based, hence the greater opportunity for initiation therein) and diabetes prevalence (which may in turn reflect geography), the populations were broadly similar.

Multiple events and mortality
Of the 1449 patients experiencing events, 905 (62.5%) experienced a single event during the study period. The distribu-

Table 1 | Characteristics of the study cohort

Factor	CVE within 2 years of HD initiation		All (*n* = 6308)
	Yes (*n* = 1449)	No (*n* = 4859)	
Region, n (%)			
West	742 (51.2)	2908 (59.8)	3650 (57.9)
East	707 (48.8)	1951 (40.2)	2658 (42.1)
Age (years)			
Mean ± s.d.	69.0 ± 11.8	63.1 ± 15.0	64.5 ± 14.5
Gender, n (%)			
Female	552 (38.1)	1995 (41.1)	2547 (40.4)
Male	895 (61.8)	2860 (58.9)	3755 (59.5)
Missing	2 (0.1)	4 (0.1)	6 (0.1)
Marital status, n (%)			
In a relationship	796 (54.9)	2744 (56.5)	3540 (56.1)
Not in a relationship	388 (26.8)	1099 (22.6)	1487 (23.6)
Missing	265 (18.3)	1016 (20.9)	1281 (20.3)
Smoking status, n (%)			
Non-smoker	514 (35.5)	1787 (36.8)	2301 (36.5)
Former	321 (22.2)	742 (15.3)	1063 (16.9)
Current	111 (7.7)	373 (7.7)	484 (7.7)
Missing	503 (34.7)	1957 (40.3)	2460 (39.0)
Body mass index (kg/m^2)			
Mean ± s.d.	27.1 ± 15.0	26.7 ± 11.2	26.8 ± 12.3
Missing, n (%)	373 (25.7)	1633 (33.6)	2006 (31.8)
Pre-dialysis disease history, n (%)			
CAE	310 (21.4)	522 (10.7)	832 (13.2)
CBE	172 (11.9)	270 (5.6)	442 (7.0)
CHFE	150 (10.4)	281 (5.8)	431 (6.8)
PAE	160 (11.0)	244 (5.0)	404 (6.4)
SCE	3 (0.2)	4 (0.1)	7 (0.1)
Diabetes	535 (36.9)	1274 (26.2)	1809 (28.7)
Atrial fibrillation	68 (4.7)	150 (3.1)	218 (3.5)
Hypertension	721 (49.8)	2257 (46.4)	2978 (47.2)
Dyslipidemia	131 (9.0)	360 (7.4)	491 (7.8)
Chronic kidney disease etiology, n (%)			
Hypertension/vascular	302 (20.8)	711 (14.6)	1013 (16.1)
Glomerulonephritis	89 (6.1)	500 (10.3)	589 (9.3)
Diabetic nephropathy	439 (30.3)	972 (20.0)	1411 (22.4)
Tubulointerstitial	147 (10.1)	514 (10.6)	661 (10.5)
Polycystic kidney disease	50 (3.5)	324 (6.7)	374 (5.9)
Miscellaneous/other	378 (26.1)	1599 (32.9)	1977 (31.3)
Invalid/missing	44 (3.0)	239 (4.9)	283 (4.5)

Abbreviations: CAE, coronary artery event; CBE, cerebrovascular event; CHFE, congestive heart failure event; CVE, composite cardiovascular event; HD, hemodialysis; PAE, peripheral arterial event; SCE, sudden cardiac event.
NB Tercile and quartile cut-offs supplied in Supplementary Table S5 online.

tion of first constituent events was broadly similar to all constituent events (coronary artery event, CAE: 26.5% vs. 28.8%; peripheral arterial event, PAE: 18.3% vs. 24.8%; congestive heart failure event, CHFE: 23.9% vs. 20.0%; cerebrovascular event, CBE: 17.7% vs. 19.6%), with the exception of sudden cardiac event, SCE (13.6% vs. 6.9%). This was largely due to the exceptionally high mortality experienced by this patient group, with 114 of 123 patients (92.7%) dying within 7 days of a first SCE (mostly consisting of sudden cardiac death events) compared with 191 of 782 patients (24.4%)

experiencing other first constituent events. The number of events experienced by the 544 patients with multiple events ranged from 2 to 12, but most patients experienced 2 or 3 (with these values forming the interquartile range). As expected, associated mortality was lower, with 188 deaths occurring within 7 days of the 956 subsequent events (19.7%), but subsequent SCE events were still temporally associated with high mortality (29/40; 72.5%). When considered sequentially, subsequent events fell within the same constituent event class in 522 instances (54.6%), but only the same ICD-10 block in 374 instances (39.1%), and both shared the same ICD-10 code in 289 instances (30.2%). The median time between a subsequent event and its predecessor was 19 days (interquartile range 1–114 days); when the subsequent event occurred on the same day ($n = 216$) it was a code from the same event class in 77 instances (35.6%), the same block in 33 instances (15.3%), but never the same code, possibly due to the fact that a specific code on 1 day was only counted once.

Rates of CVE

Table 2 shows first- and second-year rates of composite CVE and five different CVE categories for all study patients and for those initiating dialysis within or outside FME. The first-year rate of composite CVE was 30.2 per 100 person-years (PYs) and the second-year rate was 19.4 per 100 PYs. Individual CVE constituent rates were generally higher during the first year compared with the second year. In patients initiating HD outside FME, the composite CVE rate was lower. This difference was largely driven by differences in the more common CAE and CHFE, but the event rates of the three other categories also tended to be lower in those initiating outside FME.

Figure 1 shows weekly composite CVE rates during the first year after HD initiation. The CVE rate peaked sharply during week 1, when it was more than 5-fold higher than during week 2 (rate ratio (RR) 5.10 (95% confidence interval (CI), 3.95–6.59)) and subsequently declined until week 4 to achieve a relatively stable level during the remainder of the first year. Monthly rates for the composite CVE and the five different CVE constituents are illustrated in Figure 2. The temporal pattern was very similar for CAE, CHFE, PAE, and CBE, all of which showed highest incidence rates during the first month. The event rate during month 1 was highest for CAE (35.4 per 100 PY), followed by CHFE (28.2 per 100 PY), PAD (22.6 per 100 PY), and CBE (15.1 per 100 PY). To define periods of elevated risk (high-risk period), monthly event rates during year 1 were related to the average event rate during year 2 (Table 3). Although the overall CVE high-risk period was sustained until month 5 after dialysis initiation, the risk for CBE and PAE was increased during the first month, but not the second month, the risk for CAE was increased during the first 2 months, and the risk for CHFE until month 4. The event RR was particularly high for CHFE, partly because the CHFE event rate during the second year was lower than that for several other CVEs. The risk for PAE was increased again during months 3–5 and 10. In contrast to other CVE categories, the incidence of SCE followed a different pattern, with no early peak and a significant increase compared with year 2 only in month 8.

Risk factor analysis

Figure 3 shows the results of univariate analyses testing the association between demographic findings, patient history, clinical findings, and dialysis parameters for the high-risk and post high-risk periods (actual data in Supplementary Table S2 online).

Table 2 | Rates of composite CVE and CVE constituents during the first and second year in patients overall as well as in those initiating dialysis within Fresenius Medical Care dialysis centers in Europe (FME) and outside FME facilities (Non-FME)

Subset	Event	Groups of Patients, Events, Person-years at Risk and Rate per 100 Person-years (Rate (95% CI))					
		First Year			Second Year		
		Events	Person-years	Rate (95% CI)	Events	Person-years	Rate (95% CI)
All	CVE	1627	5396.6	30.2 (28.7–31.7)	796	4108.1	19.4 (18.1–20.8)
	CAE	478	5396.6	8.9 (8.1–9.7)	218	4108.1	5.3 (4.6–6.1)
	CHFE	348	5396.6	6.5 (5.8–7.2)	136	4108.1	3.3 (2.8–3.9)
	PAE	418	5396.6	7.8 (7.0–8.5)	183	4108.1	4.5 (3.8–5.2)
	CBE	288	5396.6	5.3 (4.7–6.0]	187	4108.1	4.6 (3.9–5.3)
	SCE	95	5396.6	1.8 (1.4–2.2)	72	4108.1	1.8 (1.4–2.2)
FME	CVE	1129	3392.6	33.3 (31.4–35.3)	563	2561.8	22.0 (20.2–23.9)
	CAE	346	3392.6	10.2 (9.2–11.3)	141	2561.8	5.5 (4.6–6.5)
	CHFE	241	3392.6	7.1 (6.2–8.1)	104	2561.8	4.1 (3.3–4.9)
	PAE	300	3392.6	8.8 (7.9–9.9)	152	2561.8	5.9 (5.0–7.0)
	CBE	182	3392.6	5.4 (4.6–6.2)	120	2561.8	4.7 (3.9–5.6)
	SCE	60	3392.6	1.8 (1.4–2.3)	46	2561.8	1.8 (1.3–2.4)
Non-FME	CVE	498	2004.0	24.9 (22.7–27.1)	233	1546.3	15.1 (13.2–17.1)
	CAE	132	2004.0	6.6 (5.5–7.8)	77	1546.3	5.0 (3.9–6.2)
	CHFE	107	2004.0	5.3 (4.4–6.5)	32	1546.3	2.1 (1.4–2.9)
	PAE	118	2004.0	5.9 (4.9–7.1)	31	1546.3	2.0 (1.4–2.9)
	CBE	106	2004.0	5.3 (4.3–6.4)	67	1546.3	4.3 (3.4–5.5)
	SCE	35	2004.0	1.8 (1.2–2.4)	26	1546.3	1.7 (1.1–2.5)

Abbreviations: CAE, coronary artery event; CBE, cerebrovascular event; CHFE, congestive heart failure event; CI, confidence interval; CVE, composite cardiovascular event; FME, Fresenius Medical Care dialysis centers in Europe; PAE, peripheral arterial event; SCE, sudden cardiac event; FME and Non-FME refers to the initiation of dialysis healthcare environment.
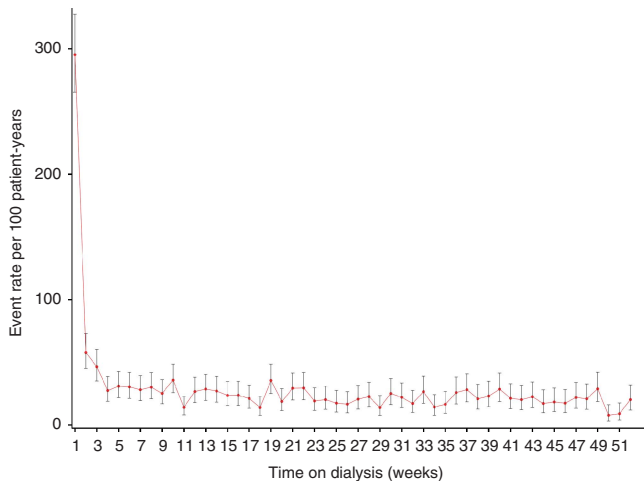
Figure 1 | Weekly event rates for the composite cardiovascular events.

For most parameters we found consistency between the direction of association during the high-risk and the post high-risk period. Factors that were associated with increased risk during both periods included increasing age, treatment in Eastern Europe, former smoking, history of CVE, diabetes, or atrial fibrillation, as well as diabetic and vascular nephropathy as underlying disease. On the other hand, several dialysis session–related parameters were associated with either increased or decreased risk during the high-risk period, but not during the post high-risk period. Low weekly dialysis dose, low predialysis blood pressure, and lower blood flow were associated with increased risk during the high-risk period only, whereas catheter use and higher net ultrafiltration were associated with reduced risk during the high-risk period only. The results for the constituent CVE were generally consistent with the composite CVE, but with less statistical power to detect significant differences (Supplementary Table S3 online).

Multivariate analysis showed the independent association between age, patient history, and dialysis parameters with CVE in the high-risk period (Table 4; detailed data in Supplementary Table S2 online). Low or high cumulative weekly dialysis dose, high pre-dialysis systolic blood pressure, lower blood flow, and lower net ultrafiltration were associated with high early CVE risk. Only traditional CV risk factors (increasing age, smoking, and CVE history) were independently associated with CVE outside the high-risk period.

Additional analyses were undertaken to examine whether the association between dialysis parameters and CVE in the high-risk period was driven by differences in patients initiating dialysis in FME facilities or elsewhere (Supplementary Figure S2 online) or by history of CVE (Supplementary Figure S3 online). Despite restricted patient populations, results were generally consistent, suggesting that these factors were not major drivers for our findings.

As we did not have data on pre-dialysis care, we used information on the use of graft and/or fistulas during the early

dialysis period (30 days) as a surrogate for a planned dialysis start. The proportion of patients experiencing an event was lower among those patients initiating within FME in whom graft/fistula use was documented compared with those in whom this was not the case (20.1% vs. 29.7%). However such a difference was not found in patients initiating outside FME (20.7% vs. 20.9%). Moreover, the monthly CVE pattern in the FME and non-FME 'graft/fistula' and 'no graft/fistula' patient groups was similar, suggesting that a planned start cannot prevent an increase in events soon after HD initiation.

DISCUSSION

The prevalence of most manifestations of CVD increases with declining renal function and is particularly high in patients on dialysis.[9,14,15] The current study shows that the immediate period following dialysis initiation is a very high CV risk period, characterized by a much higher rate of major CVE than the remainder of the first 2 years. Incidence rates that were at least 3- and up to 8-fold higher than during the second year on dialysis were found for vascular events affecting coronary, cerebral, and peripheral arterial beds as well as heart failure during the first month on dialysis. Analysis of the composite CVE rate, which allowed a more granular analysis of temporal trends showed, in fact, that the first week of HD was associated with maximum CVE risk.

Although, to our knowledge, no previous studies have determined CVE rates after dialysis onset, our findings are consistent with several investigations that have highlighted an increased mortality during the first year on dialysis[4,9,16] and in particular during the first 90[2,17] or 120[3,7] days. Although data on peak mortality rates are somewhat variable, one large cohort study of over 300,000 patients observed highest mortality rates within the first 2 weeks,[5] which corroborates our notion of an early high-risk period. Multiple causes may contribute to early mortality on dialysis, but the majority are considered of CV origin,[3,6] which is also consistent with our observation of elevated CVE rates after dialysis initiation. Several traditional risk factors, which we found to be associated with CVE in the early phase after dialysis initiation, such as age, smoking history, and CVE history were also identified to be associated with early mortality in HD patients.[2,3] Although we observed a substantial overall mortality rate of 20% within 1 week following a CVE, the majority of observed CVEs were not immediately fatal, indicating a substantial increase in morbidity early after dialysis initiation.

Theoretically, at least two different reasons may underlie the increased rate of CVE following the onset of dialysis. First, deterioration of renal function and/or the signs and symptoms resulting in a decision to initiate dialysis may be prodromal signs of the subsequent event. This appears possible, e.g., for CHF events, but is less plausible for vascular events, such as CBE, PAE, or CAE. The second and alternative explanation would be that the initiation of dialysis triggers CVE. In fact, the HD procedure itself has been recognized to induce myocardial stunning and contractile dysfunction,[18,19] endothelial dysfunction,[20] oxidative stress,[21] and inflammation.[22]
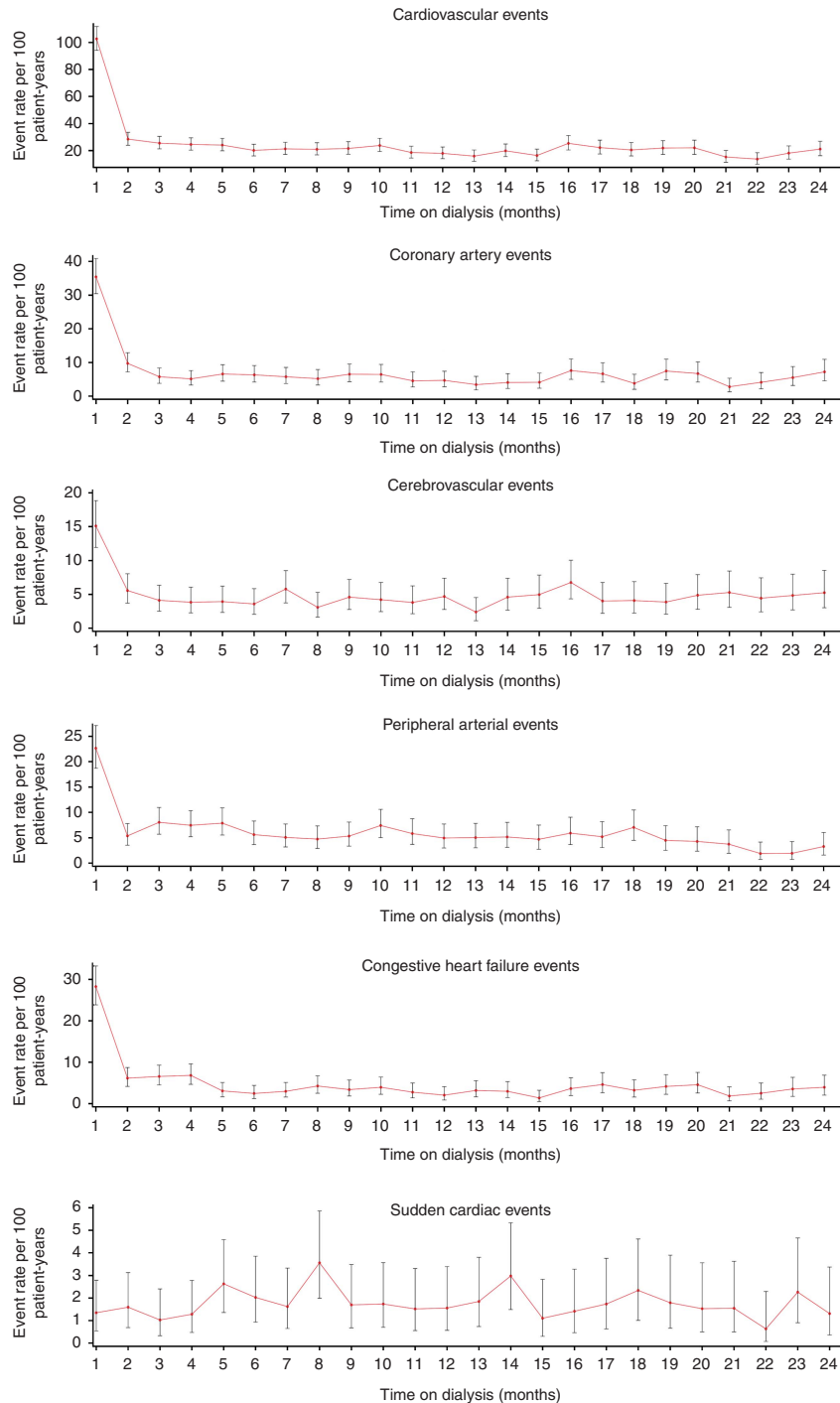
Figure 2 | Monthly event rates for the composite cardiovascular events and constituent events.

Additional evidence suggests a direct temporal association of CVE with the dialysis procedure. Thus, about one-third of all strokes in dialysis patients were found to occur during or shortly after HD treatment.[12,23] Mortality rates and CVE admission rates in a large US study of dialysis patients were found to be associated with the dialysis schedule, with highest rates on the day following the long interval.[24] Irrespective of what causes temporal associations between dialysis and CVE, additional factors must play a role that

increases the sensitivity during the first weeks and months of dialysis. Although a decline in mortality rates may partly be explained by the fact that high-risk patients die early and less severely ill patients survive, similar considerations do not sufficiently explain why the incidence rates for a variety of different CVEs decline in parallel over time. The majority of associations between risk factors and CVE were similar for the high-risk and the post high-risk period, and we found little evidence for factors that are only associated with CVE during

Table 3 | High-risk periods for composite CVE and constituent events

Month	Rate ratio (95% confidence interval)					
	CVE	CAE	CHFE	PAE	CBE	SCE
1	**5.32 (4.76–5.94)**	**6.73 (5.52–8.20)**	**8.57 (6.78–10.84)**	**5.09 (4.03–6.42)**	**3.28 (2.52–4.27)**	0.79 (0.36–1.71]
2	**1.47 (1.23–1.76)**	**1.85 (1.36–2.52)**	**1.87 (1.27–2.76)**	1.21 (0.80–1.81)	1.21 (0.81–1.80)	0.92 (0.44–1.92)
3	**1.32 (1.09–1.60)**	1.10 (0.74–1.63)	**2.00 (1.36–2.94)**	1.81 (1.28–2.55)	0.90 (0.57–1.42)	0.60 (0.24–1.48)
4	**1.27 (1.04–1.54)**	0.97 (0.64–1.48)	**2.07 (1.41–3.04)**	1.67 (1.17–2.40]	0.83 (0.51–1.35]	0.74 (0.32–1.71)
5	**1.25 (1.02–1.52)**	1.25 (0.85–1.83)	0.93 (0.54–1.61)	1.77 (1.24–2.53)	0.86 (0.53–1.39)	1.53 (0.83–2.82)
6	1.04 (0.83–1.29)	1.20 (0.81–1.78)	0.75 (0.41–1.39)	1.27 (0.83–1.92)	0.78 (0.47–1.31)	1.18 (0.59–2.36)
7	1.10 (0.89–1.36)	1.10 (0.72–1.66)	0.91 (0.52–1.61)	1.14 (0.73–1.78)	1.26 (0.83–1.91)	0.94 (0.43–2.04)
8	1.08 (0.87–1.35)	0.99 (0.64–1.54)	1.30 (0.79–2.12)	1.07 (0.67–1.69)	0.67 (0.38–1.18)	**2.07 (1.18–3.61)**
9	1.12 (0.90–1.39)	1.24 (0.83–1.86)	1.03 (0.59–1.79)	1.20 (0.77–1.87)	1.00 (0.62–1.61)	0.99 (0.45–2.14)
10	1.23 (1.00–1.52)	1.22 (0.82–1.84)	1.20 (0.72–2.02)	1.67 (1.14–2.46)	0.92 (0.56–1.51)	1.01 (0.46–2.19)
11	0.96 (0.75–1.22)	0.87 (0.54–1.40)	0.85 (0.46–1.56)	1.31 (0.85–2.02)	0.83 (0.49–1.40)	0.88 (0.38–2.03)
12	0.93 (0.72–1.18)	0.89 (0.55–1.44)	0.63 (0.31–1.29)	1.11 (0.69–1.78)	1.02 (0.63–1.65)	0.90 (0.39–2.08)

Abbreviations: CAE, coronary artery event; CBE, cerebrovascular event; CHFE, congestive heart failure event; CVE, composite cardiovascular event; PAE, peripheral arterial event; SCE, sudden cardiac event.
Boldface data represent the high-risk periods, during which the event rate remained significantly higher than the average event rate of the second year.
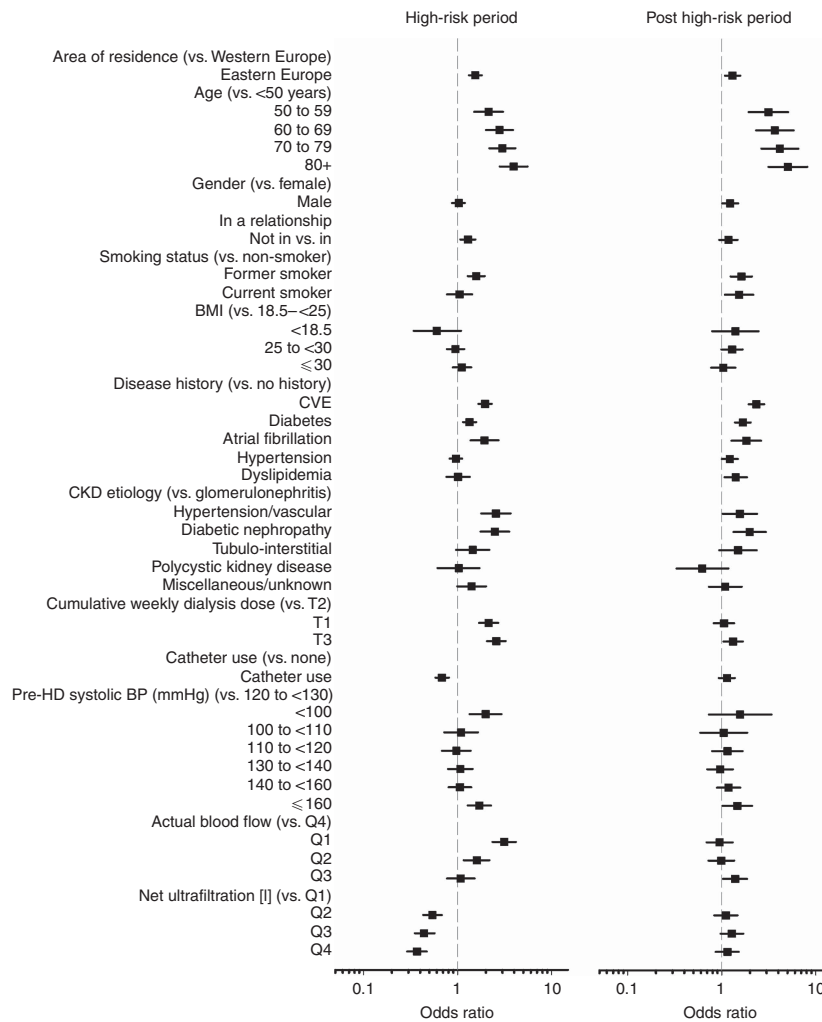
Figure 3 | Factors associated with composite cardiovascular events in the high-risk (left) and post high-risk (right) periods. Univariate analysis (actual data shown in Supplementary Table S2 online). BMI, body mass index; CVE, cardiovascular events; HD, hemodialysis.

the high-risk period. For some aspects of CVD history at baseline and specific etiologies of kidney disease, multivariate analysis showed associations only during the early high-risk period, and it is plausible that these factors lose their relevance with time. In contrast to an early peak observed for other CVE constituents, SCE was the only type of event that followed a different pattern with no clear trend in incidence rates during the first 2 years. We cannot explain this

Table 4 | Factors associated with composite CVE in the high-risk and post high-risk periods (summarized multivariate analysis; actual data shown in Supplementary Table S1 online)

Group	High-risk period	Post high-risk period
Demographic	Increasing age	Increasing age
	Former smoker	Former smoker
		Current smoker
Clinical	History of cardiovascular event	History of cardio-vascular event
	History of atrial fibrillation	
	CKD etiology of hypertension/vascular disorders	
	CKD etiology of diabetic nephropathy	
Dialysis	Higher or lower cumulative weekly dialysis dose	
	High pre-dialysis systolic blood pressure	
	Lower actual blood flow	
	Lower net ultrafiltration	

Abbreviations: CKD, chronic kidney disease; CVE, cardiovascular event.

difference but it is important to note that the accuracy of SCE diagnosis is likely to be lower than that for other CVEs.[15]

Our study has several limitations. Primarily, overall event rates were lower in patients initiating outside of FME facilities. The reasons for this difference remain speculative, but, given that many events occur within the first week after dialysis initiation, it is possible that fatal and non-fatal events occurred in patients initiating HD outside FME prior to possible capture in the study, thus resulting in a healthier sub-cohort (survival bias). Other differences related to patient selection and treatment, however, cannot be excluded. Despite this uncertainty, we chose to conduct further analysis with the whole study cohort, rather than only those patients initiating within FME, recognizing that this may lead to an underestimation of event rates. Sensitivity analyses, examining the effect of initiating within FME facilities or elsewhere, showed that the inclusion of these patients had a minimal impact on our risk factor analysis. Furthermore, CVEs were assessed on the basis of ICD-10 codes and were not adjudicated. In particular, distinguishing between heart failure and volume overload is inherently difficult. We also do not have data on several parameters that may have implications for the interpretation of CVEs, including first presentation to nephrologists, the level of renal function at dialysis initiation, the specific indication for starting dialysis, or residual renal function.[25] As patients were enrolled at presentation to a dialysis provider, we are unable to compare event rates after dialysis initiation with event rates during the pre-dialysis period. The AROii study represents a random sample drawn from European FME centers to minimize selection bias, but the findings may not be generalizable for patients under the care of other providers. The strength of the study includes the prospective establishment of an incident cohort of dialysis patients, the continued coverage of patients with <7 days of dialysis vintage,[26] the broad geographic distribution across several European countries, the assessment of fatal and non-fatal events, and the possibility to assess and compare the incidence rates of a whole spectrum of CVEs over time.

Although our findings clearly show that the early period after dialysis initiation should be recognized as a high-risk period that mandates increased surveillance, the optimal mode of patient care during this period remains unclear. We observed robust associations between CVE during the early high-risk period with some dialysis-related parameters, including higher and lower weekly dialysis dose, low actual blood flow, and low net ultrafiltration. The latter observations might suggest intensifying dialysis regimens early after dialysis initiation rather than gradually increasing treatment intensity over time. However, the association does not necessarily imply causality, and, despite being statistically independent, these parameters might also be surrogates for patients with compromised CV function, in whom neither a higher dialysis blood flow nor a higher rate of ultrafiltration could be achieved. We were surprised to observe that catheter use was associated with reduced risk during the high-risk period, as previous studies have consistently shown that catheter use is associated with early mortality.[3,6] A large portion of catheter-associated mortality is due to infections,[27,28] and the association with CV morbidity may be less strong. In any case, the finding was not confirmed in multivariate analysis, suggesting that it is due to confounding by other factors. Unfortunately, uncertainty also extends to acute management of CV complications and secondary prevention in patients on HD.[15,29] Of interest, it has been reported that a dedicated program of intensive patient education, evaluation, and early clinical intervention in patients new to dialysis reduced mortality within the first 120 days by 31% in a case–control study,[30] suggesting that a significant improvement in prognosis is feasible.

Finally, our findings also have to be considered in the context of an ongoing debate about the optimal timing of dialysis initiation and alternative treatment strategies. Prognosis of patients on dialysis is inversely associated with the level of residual renal function at dialysis initiation;[31] however, strong confounders of this association have been identified.[32] Moreover, controlled studies and interventional trials in aggregate favor a later rather than an earlier dialysis initiation.[33,34] There is an increasing appeal for shared decision making for dialysis initiation, based on evaluation of risks, benefits, quality of life impact, and prognosis.[35,36] Based on our findings we believe that an increased risk for CVE after dialysis initiation should be taken into account in such deliberations.

MATERIALS AND METHODS
The ARO CKD research initiative began in 2007, with the purpose of improving HD patient outcomes in Europe through better understanding of patient morbidity and risk factors.[37] The second ARO cohort, AROii, comprises adult subjects presenting at 1 of over 300 participating FME facilities in 14 European countries and Turkey between 1 January 2007 and 31 December 2009. Closed-cohort by design, AROii comprises incident HD patients (<183 days since commencing HD) with no history of renal transplantation. Data, comprising detailed patient-level information on medical and drug history, and longitudinal records of biochemical measurements and medications, are captured electronically via the validated FME European Clinical Database and supplied on a quarterly basis.

All ethical and regulatory obligations concerning the use of patient data are met at each participating site. The patient population was restricted further in the current study to include patients with a dialysis vintage of <7 days on admission to an FME clinic, or who initiated within 365 days of admission. All patients were required to have at least one dialysis session in FME facilities.

Initial descriptive statistics were analyzed to describe the study population at baseline and the distributions of the study confounders. Continuous variables were described using mean and s.d., median, 25th and 75th percentiles, and minimum and maximum values. Skewed variables were described using a median and range, or categorized into meaningful categories at which point categorical data analysis was applied. Categorical data were reported as counts and frequencies.

The primary end point for analyses, the composite CVE, comprised fatal or non-fatal constituent CAE, CBE, PAE, CHFE, and SCE based on ICD-10 coded comorbidities data (Supplementary Table S4 online). Crude event rates were calculated for each week (for the composite CVE) and month of dialysis vintage (for all outcomes) during the first 2 years. In each instance, patients accrued time at risk from the beginning of the month of interest until they experienced the event of interest or were censored (lost-to-follow-up (>45 days without continuous dialysis at an FME facility), renal transplantation, or the end of that month, whichever came first). The event rate, $\hat{\rho}$, was estimated as:

$$\hat{\rho} = \frac{Y}{e}$$

where Y is the observed number of events, and e is the exposure period in PY.[38] Exact 95% Poisson CIs were derived and presented as:

$$Y_1 = \frac{\chi^2_{2Y,\alpha/2}}{2e} \qquad Y_u = \frac{\chi^2_{2(Y+1),1-\alpha/2}}{2e}$$

where Y is the observed number of events, Y_1 and Y_u are lower and upper CIs for Y, respectively, and $\chi^2_{\nu,\alpha}$ is the χ^2 quartile for upper tail probability $\alpha(0.05)$ on ν degrees of freedom.[39] An objective approach was taken to define the high-risk period, where RRs were calculated for each month in the first year using the second-year rate as the reference time period. The high-risk period was defined as the period during which the risk was significantly elevated as compared with the second year. In other words, the high-risk period extended to the point where the lower CI for the RR included one. The post high-risk period represented the period from the end of the high-risk period until the end of the first year. RRs were calculated on the basis of the formula:

$$RR = \frac{Y_1/e_1}{Y_2/e_2}$$

where Y_1 and Y_2 are the number of events in any given month and the second year, respectively, and e_1 and e_2 are the PYs at-risk for the same time points; 95% CIs for the RR were calculated on the basis of the formula $\log(RR) \pm 1.96 \times SE[\log(RR)]$, where $SE[\log(RR)]$ (the standard error of the log RR) was calculated[40] as:

$$\sqrt{1/Y_1 + 1/Y_2}$$

Logistic regression models were fitted to the data to determine separately potential predictors of events in high-risk and post high-risk periods. Patients experiencing the outcome of interest (coded '1' in the outcome variable) were compared with patients who did not (coded '0' in the outcome variable) as of the end of the period, with odds ratios and 95% CIs calculated for each explanatory variable (Table 1). Multivariate logistic regression was applied to control for confounding.

Potential predictors—those associated with the outcome at the 95% level—were added and removed from the model in a stepwise manner, where 10% and 5% significance levels were used to determine variable entry and retention, respectively. Logistical regression models rather than a Cox proportional hazards model–based approach were used, as patients were defined by their outcome (rather than exposure). Moreover, regression coefficients obtained from both approaches are similar, when—as in our study—the follow-up time is short.[41]

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SUPPLEMENTARY MATERIAL
Figure S1. Patient's dialysis vintage on recruitment to the AROii cohort. Insert shows the hemodialysis peri–initiation period in detail.
Figure S2. Factors associated with composite CVE in the high–risk period by (FME) initiation status (univariate analysis).
Figure S3. Factors associated with composite CVE in the high–risk period by history of CVE (univariate analysis).
Table S1. Characteristics of the study population by initiation in a Fresenius Medical Care European (FME) facility or elsewhere.

Table S2. Factors associated with composite CVEs in the high-risk and post high-risk periods (univariate and multivariate analysis). Estimates where 95% confidence intervals do not include one are emboldened.
Table S3. Factors associated with the constituent events in the high-risk and post high-risk periods (univariate analysis). Estimates where 95% confidence intervals do not include one are emboldened. Depending on the limited number of observed sudden cardiac events (SCEs), the analysis is not provided for this constituent event category.
Table S4. Cardiovascular disease event codes.
Table S5. Quartile (25%, 50% & 75%) and Tercile (33% & 67%) cut-offs applied in the study.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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