MORTALITY REDUCTION BY ONLINE-HEMODIAFILTRATION

a cause-specific analysis

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Abstract

Background. From an individual participant data (IPD) meta-analysis from four RCTs, comparing HD with online-HDF (ol-HDF), previously it appeared that HDF decreases all cause mortality by 14% (25;1) and fatal cardiovascular disease (CVD) by 23% (39; 3). Significant differences were not found for fatal infections and sudden death. So far, it is unclear, however, whether the reduced mortality risk of HDF is only due to a decrease in CVD events and if so, which CVD in particular is prevented, if compared to HD.

Methods. The IPD-base was used for the present study. HRs and 95% CIs for cause specific mortality overall and in tertiles of the convection volume were calculated using the Cox Proportional hazard regression models. Annualized mortality and numbers needed to treat (NNT) were calculated.

Results. Besides 554 patients dying from CVD, fatal infections and sudden death, 215 participants died from 'other causes', such as withdrawal from treatment and malignancies. In this group, the mortality risk was comparable between HD and ol-HDF patients, both overall and in tertiles of the convection volume. Subdivision of CVD mortality in fatal cardiac, non-cardiac and unclassified CVD, showed that ol-HDF was only associated with a lower risk of cardiac casualties [0.64(0.61;0.90)]. Annual mortality rates also suggest that the reduction in CVD death is mainly due to a decrease in cardiac fatalities, including both ischemic heart disease and congestion. Overall, 32, respectively 75 patients need to be treated by high volume HDF (HV-HDF) to prevent one all cause, respectively CVD death/year.

Interpretation. The beneficial effect of ol-HDF on all cause and CVD mortality appears mainly due to a reduction in fatal cardiac events, including ischemic heart disease as well as congestion. In HV-HDF the NNT to prevent one CVD death is 75/year.

INTRODUCTION

Compared to the healthy population, hemodialysis (HD) patients have a greatly increased mortality risk (1). Since retention of uremic toxins in the middle-molecular weight (MMW) range has been implicated in the poor clinical prospects of these patients, removal by convection through high-permeable (high-flux) dialyzers may improve survival. Three large randomized controlled trials (RCT), however, did not demonstrate an overall favorable effect of high-flux dialyzers over low permeable (low-flux) devices, which remove only small compounds by diffusion (2-4). Yet, in these RCTs a trend was observed towards a better clinical outcome for selected patient groups who were treated with high-flux HD. Hence, it is possible that the amount of convective transport, which occurs within the dialyzer in high-flux HD (<10L/session) (5), was too small to obtain a clinical noticeable effect.

To retain the diffusive capacity of HD and augment the convection volume, hemodiafiltration (HDF) was developed(6). In this modality, plasma water is extracted from the blood, which, however, must be replaced by a sterile endotoxin-free substitution fluid. Originally, replacement fluid was administered in bags, which restricted its volume (< 13L/session) (7) and prevented implementation on a large scale. With the introduction of modern HDF machines and water treatment systems, which allow the online production (ol-HDF) of large amounts of sterile and endotoxin free substitution fluid (8), much larger convection volumes (>23L/session) became accessible for every day clinical practice.

Based on several observational studies (7;9-11) suggesting a superior clinical outcome for patients who were treated with HDF, three large RCTs, comparing HD with ol-HDF, were conducted (12-14). Despite inconsistent outcomes of the individual studies, a recently published individual participant data (IPD) analysis, based on these three studies and a fourth not yet published French investigation, indicated that both the all cause and cardiovascular (CVD) mortality risks were significantly reduced by ol-HDF (15). These results were confirmed in a latest survey of the French Rein Registry (16). The IPD analysis also showed that the mortality risks for infections and sudden death were not different for HD and ol-HDF patients. Moreover, it appeared that the relative risk reduction in the all cause and CVD mortality risks was greatest for patients who were treated with high volume HDF (HV-HDF).

Since in our first IPD analysis the total number of deaths was markedly higher than the summed mortality from CVD, infections and sudden death, a considerable number of patients died from other causes. Hence, it is not quite clear whether the reduction in all cause mortality is exclusively due to a decline in fatal CVD events or also to a decrease in non-CVD fatalities. In case of a selected reduction in fatal CVD events the question arises whether the beneficial effect of ol-HDF is caused by a decrease in cardiac or non-cardiac fatalities, or both. If, for example, the risk reduction in all cause

mortality is largely due to a decrease in fatal cardiac events, it might be helpful for prevention and management to know which heart disease in particular benefits from treatment with ol-HDF. Finally, from a public health care perspective, it is also important to know the number of patients needed to be treated (NNT) by ol-HDF to prevent one death. The aim of the present study was therefore to address these issues and to examine the relationship between the effects of ol-HDF versus HD on cause-specific mortality endpoints.

MATERIAL AND METHODS

Study design

For the present analysis, data were used from the individual participant data (IPD) base of four large multicentre RCTs, comparing the effects of ol-HDF with HD in adult patients (15). A detailed description of the study designs, patient eligibility criteria, and treatment procedures of each of the individual studies has been provided elsewhere (12-14).

Study population, study endpoint and follow up

Besides the subdivision of all cause mortality in CVD mortality, fatal infections and sudden death a group 'other causes' was created, including death due to malignancies and patients who discontinued dialysis treatment, as defined within the individual studies. In addition, we repeated the analysis by adding sudden death to the group of CVD mortality(17). Sudden death was defined as a sudden unexpected fatality occurring within an hour of symptom onset, or un-witnessed, unexpected death in patients to be well in the past 24 hours. Then we investigated CVD mortality, by splitting up this fraction in fatal *cardiac* events, such as myocardial infarction (MI), arrhythmias and 'chronic heart failure/ fluid overload', *non-cardiac* fatalities, including stroke and peripheral arterial disease and *unclassified CVD* mortality, consisting of fatalities which were denoted in the RCTs as CVD, but without any further specificity. As congestive heart failure and fluid overload are difficult to distinguish in HD patients, in the present analysis both conditions were brought together under the heading 'congestion'. Subsequently, we compared the individual cardiac death causes between HD and ol-HDF. The HRs for cardiac causes were assessed by calculating first the HR of all cardiac causes combined, and subsequently removing congestion and arrhythmia. Next, we estimated the annualized all cause and CVD mortality data/100 patient years in both groups and lastly, the patient numbers needed to treat (NNT) by ol- HDF to prevent one HD death/year, overall and in the CVD subgroup.

Data analysis

Cox proportional hazard regression models with a random effect for study were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) comparing the effect of online-HDF versus HD on the study endpoints. The dose-response association between achieved convection volume in online-HDF versus HD and clinical outcomes was examined in tertiles of the actual (on-treatment) delivered, 1.73m^2 body surface area (BSA)-standardized convection volume, and was adjusted for age, sex, albumin, creatinin, history of diabetes and previous CVD. All analyses were performed in the statistical environment R (version 2.15.3). Two-sided *p*-values and 95% CI were used for statistical

inferences. Annual mortality rates per 100 patient years were calculated by dividing the number of deaths by the total follow up in years and multiplying by 100. NNTs/year were calculated by the fraction 100/annualized mortality rate HD - annualized mortality rate ol-HDF.

RESULTS

In Table 1 the demographical and clinical patient characteristics, laboratory data and treatment-related parameters are summarized. During a mean follow up of 2.5 (1.9-3.0) years, 292 participants died of CVD, 150 of infections, 112 of sudden death and 215 of 'other causes'.

Ol -HDF and all cause and cause specific mortality

In Table 2 both the absolute patient numbers and risk ratios are presented. As reported before (15), ol-HDF reduced the risk of all cause and CVD mortality by 14% (25;1) and 23% (39;3), respectively. In absolute numbers, CVD death accounted for 71% (36/51) of the difference in all cause mortality between the two groups. The number of fatalities due to infections, sudden death and the combined group 'other causes' was comparable. The conclusions for CVD mortality did not materially alter when the group *sudden death* was included in this group.

Subdivision in tertiles of the convection volume showed a distinct pattern for all cause mortality, CVD mortality and sudden death: the larger the convection volume, the lower the associated risk (p for trend resp . 0.02, 0.07, 0.04). No such a pattern was observed for the groups consisting of fatal infections and 'other causes' of death (p respectively 0.15 and 0.74).

Ol- HDF and cardiovascular disease mortality

As also shown in Table 2, ol-HDF was associated with a lower risk of *cardiac* CVD fatalities [HR 0.64(0.61;0.90)], p=0.01] but not of *non-cardiac* CVD mortality [HR 0.92 (0.60; 1.43), p=0.73] and *unclassified* CVD mortality [HR 0.90(0.58;1.45), p=0.65]. In absolute numbers, *cardiac* death accounted for 77% (27/36) of the difference in total CVD mortality between the HD and online HDF groups.

High convection volumes appeared to be associated with a lower risk of dying from cardiac causes and unclassified CVD than a low convection volume (p for trend respectively 0.03 and 0.05). No such a pattern was observed for fatal non-cardiac CVD (p for trend=0.74). The annualized fatal events/100 patient years are shown in table 3 and figure 1.

Ol-HDF and pure 'cardiac' mortality

As shown in Table 4, the absolute numbers of myocardial infarction, arrhythmia and congestion were 38, 15 and 33 in the HD group and 24, 6 and 24, in online HDF, respectively. As for cardiac CVD, the lowest HR [0.58(0.36;0.91)] was found for the joint diagnoses myocardial infarction and arrhythmia; the addition of congestion yielded a HR of 0.64(0.45;0.90).

Ol-HDF and numbers needed to treat in tertiles of the convection volume

Note that the NNTs are presented per year. To prevent one all cause death or one fatal CVD, 61

respectively 90 patients need to be treated by ol- HDF. These figures are 32 and 75, respectively in HV-HDF (Table 3).

DISCUSSION

Previously we reported that ol-HDF reduces the all cause mortality risk of dialysis patients by 14%(25;1) and the CVD mortality risk by 23%(39;3).These data appeared even more pronounced [22% (38;2)] and 31%(53;0), respectively] when high convection volumes are applied i.e. HV-HDF (15).

What this study adds

In the present extended analysis we show first, that the beneficial effect of ol-HDF on survival indeed was most prominent for fatal CVD events. Other causes, including a combined group 'others causes' consisting of 215 fatalities of various diagnoses such as withdrawal from treatment and malignancies, did not differ between HD and ol-HDF patients. In absolute numbers, 71% of the lower all cause mortality was due to a reduction in fatal CVD. Second, , the risk of pure fatal cardiac CVD differed significantly between HD and ol-HDF, while the risk of non-cardiac CVD and un-classified CVD was comparable. In absolute numbers, 77% of the lower CVD mortality appeared to result from a reduction in cardiac deaths. Third, considering only fatal heart diseases, it appeared that the associated risk reduction was not caused by a selective decrease in just one particular fatal heart disease, but more likely by a decrease in both ischemic heart disease and congestion. Fourth, our analysis showed that 32, respectively 75 patients need to be treated by HV- HDF to prevent one all cause, respectively one CVD death/year. For comparison, the NNT to prevent one CVD death by anti-hypertensive treatment in low risk patients with mild hypertension has been estimated 82/10 years or 820/year (18).

In our prior analysis, sudden death was considered separately because a distinct pattern was observed: the larger the convective volume the lower the associated risk. Moreover, not only classical CVD events, such as cardiac arrhythmias and severe stroke, may be underlying causes of death but also other diagnoses, including lung emboli and septicemia. In this respect, it should be noted, however, that, while several arrhythmic triggers, such as large extracellular volume changes, electrolyte disturbances and autonomic imbalance in CKD patients with uremic cardiomyopathy, may contribute to the risk of sudden cardiac death (SCD), prevention with implantable cardioverter-defibrillators (ICD) did not show unequivocal beneficial results. Although two meta-analyses (19;20) and a recent large propensity-matched mortality analysis (21) suggested a survival advantage of ICD implantation in patients with mild CKD, benefit could not be demonstrated in advanced CKD and dialysis patients. Based on these data it was speculated that SCD in the latter groups of patients is resistant to the effects of ICD. Alternatively, however, it seems possible that sudden death in CKD

patients is caused less frequently by lethal arrhythmias, as suggested in several papers (22;23), but relatively more often by non-direct cardiac causes, such as severe stroke (13). Unfortunately, scarce data are available on the reasons of sudden death in dialysis patients (24). As shown in our study the risk of sudden death was similar for HD and ol-HDF patients. Since sudden death in the general population is caused mainly by coronary heart disease-associated causes (17) and should hence be considered SCD, in a secondary analysis we included patients who were classified as 'sudden death' in the group 'fatal CVD'. This modification did not materially change our main conclusions as outlined above.

Importance of online-HDF on convective transport

Why is ol-HDF associated with an improved outcome, if compared to HD? As mentioned before, retention of MMW and protein-bound uremic toxins have been associated with morbidity and mortality in CKD patients (25;26). Until now, however, no specific uremic toxin has been identified that is exclusively responsible for the poor clinical prospects of these patients. At this point, however, it might be noteworthy to mention that the levels of fibroblast growth factor (FGF) 23, which are massively increased in patients with advanced CKD and correlate with left ventricular hypertrophy (LVH) (27) and death (28), are highly efficient removed by HDF (29). Hence, lowering of this substance may favorably influence the clinical course in these patients. So far, however, definite proof is lacking that improvement of the 'milieu interieur' will lead to a better clinical outcome. Yet, enhanced removal of MMW and other uremic toxins by an augmented convective transport is an appealing explanation for the beneficial effects of ol-HDF on survival.

Importance of online HDF on intra-dialytic hemodynamic stability

Alternatively, HDF may improve intra-dialytic hemodynamic instability (30;31), which is the most important acute CVD complication in intermittent dialysis therapies and related to end-organ ischemia and mortality (32). Since micro-circulatory dysfunction is a common feature in ESKD patients (33), intradialytic hypotension (IDH) may further compromise the perfusion and functioning of vital organs during treatment. Indeed, well-designed studies have shown that IDH contributes to reversible regional myocardial stunning (34;35), splanchnic hypoperfusion and endotoxemia (36), as well as cerebral dysfunctioning (37). In studies comparing HD with HDF, IDH was mitigated or even absent during HDF (38). Interestingly, when cooled dialysate was used in HD, the effect on IDH was comparable to HDF (39). Thus, substantial evidence exist for an important effect of thermal balance as a contributing factor for the improved hemodynamic stability during HDF. Therefore, apart from

enhanced uremic toxin removal by convective transport, HDF may preserve vital organ functioning by a superior intra-dialytic hemodynamic stability (40).

Notably, the results of this analysis were obtained despite the potential negative role of high flow fistula on cardiac performance (41). Previously, (42) we described a mean blood flow of 387 ml/min in HV-HDF (versus 335ml/min in the HD group), which was associated with the lowest mortality risk (15). In this respect it is noteworthy to refer to an echocardiographic evaluation in 326 CONTRAST participants. From this analysis it appeared that the functional and structural changes of the left ventricle which occurred in the group of HD patients, were mitigated or virtually absent in patients who were treated with ol-HDF (43).

Is the reduced risk of cardiac mortality depending on the convection volume?

Whatever the mechanism(s), the beneficial effect of ol- HDF on mortality appears especially pronounced in HV-HDF (15). Therefore, this extended cause specific analysis was also performed in tertiles of the convection volume. Apart from a significant trend for all cause, CVD and pure cardiac mortality, a dose-response relation was also observed for unclassified CVD mortality and sudden death: the higher the convection volume, the lower the associated risk. No such a pattern was observed for fatal infections and the group consisting of 'other causes' of death. Assuming that a large proportion of the mortality in the groups 'sudden death' and 'non-classified CVD' originates from the heart as well, it appears that the beneficial effect of a high convection volume is indeed almost exclusively due to a lower *cardiac* mortality risk. respectively

Strengths and limitations

The strength of this study is the concise and meticulous data collection from four recent RCTs, as described previously (15). As a consequence, informative censoring, due to transplantation or withdrawal alive from treatment, is negligible. As such, this IPD meta-analysis is unique, and quite different from meta-analyses based on aggregated patient data (44-46). By contrast, our IPD meta-analysis cannot correct for selective inclusion in the individual RCTs, which is obviously a limitation of this study. In addition, we did not calculate changes over time in UF rate, Kt/V, bicarbonate and Mg levels, which may be implicated in the life expectancy of our patients (47). However, since not all these parameters are available over time in the individual studies and the association of these changes on outcome was not the goal of the present study we refrained from such an analysis. Other limitations are the differences between trials in terms of study design and methodology, which we accounted for as much as possible in our statistical models. Some jargon, however, such as

unclassified CVD , which is already hard to interpret in one multicenter RTC, is even more delicate when four RCTs from different countries are combined. Furthermore, conclusions on the effects of different convection volumes on mortality are derived from *post hoc* analyses and should hence be considered with caution. Finally, the small absolute number of fatal 'cardiac' CVD events and hence the limited absolute difference between the study groups prevents firm conclusions on the protective effects of treatment with ol-HDF.

Conclusions

The most important finding of this large scale IPD meta-analysis is the predominant risk reduction of fatal CVD in ol-HDF. Other causes of death, including fatal infections and a group consisting of 'other causes' of death, such as withdrawal from treatment and malignancies, did not materially differ between HD and ol-HDF. The second most important outcome of this study is the finding that the risk of fatal non-cardiac CVD events, including stroke and peripheral artery disease, did not differ, while ol-HDF was associated with a lower risk of *cardiac* deaths. The beneficial effect of HV-HDF appears especially apparent for this type of fatality. Both a lower risk of ischemic heart disease and congestion may play a role. Interestingly, only 32 patients need to be converted from HD to HV-HDF to prevent one death from all causes and 75 to prevent one CVD death/year.

Table 1: Baseline parameters of study participants

	All (n=2793)	*HD (n=1393)*	*HDF (n=1400)*
Patient characteristics			
Females (%)	1045 (37)	528 (38)	517 (37)
Age (years)	64.1 (14.7)	64.4 (14.8)	63.8 (14.3)
BMI (after dialysis, kg/m^2)	25.2 (4.7)	25.2 (4.6)	25.2 (4.9)
Body Surface Area (m^2)	1.76 (0.22)	1.77 (0.22)	1.76 (0.22)
Systolic blood pressure (mmHg)	137.4 (22.4)	137.5 (22.8)	137.3 (22.1)
Diastolic blood pressure (mmHg)	73.7 (13.3)	73.5 (13.6)	73.9 (13.1)
Diabetes Mellitus (%)	814 (30)	402 (29)	412 (29)
History of CVD (%)	989 (35)	499 (36)	490 (35)
Laboratory data			
Hemoglobin (g/dl)	11.7 (1.6)	11.7 (1.6)	11.7 (1.6)
PTH (pmol/L)	312.9 (145; 774)	307 (147; 789)	318 (142; 752)
Calcium (mg/dl)	39.0 (4.4)	36.0 (4.8)	36.4 (4.0)
Bicarbonate (mmol/L)	22.2 (3.5)	22.2 (3.6)	22.3 (3.5)
Creatinine (mg/dl), predialysis	8.39 (2.57)	8.42 (2.63)	8.35 (2.51)
Phosphate (mg/dl)	4.76 (1.53)	4.71 (1.52)	4.79 (1.53)
B-2-microglobulin (mg/L)	27.2 (11.6)	27.7 (11.9)	26.8 (11.3)
Albumin (g/dl)	3.98 (0.41)	3.98 (0.41)	3.98 (0.41)
Cholesterol (mg/dL)	159 (48)	160 (49)	158 (47)
CRP (mg/L)	3.48 (0.90;8.60)	3.47 (0.89; 8.50)	3.50 (0.94; 8.70)
Treatment related parameters			
Dialysis vintage (months)	33 (15; 64)	34 (15; 65)	32 (14; 64)

Vascular access (AVF)	2376 (85)	1175 (84)	1201 (86)
Dialysis single-pool Kt/V	1.52 (0.31)	1.50 (0.30)	1.51 (0.32)
Duration of session (min)	233 (20)	233 (20)	233 (20)
Blood flow (ml/min)	337 (66)	335 (66)	336 (66)

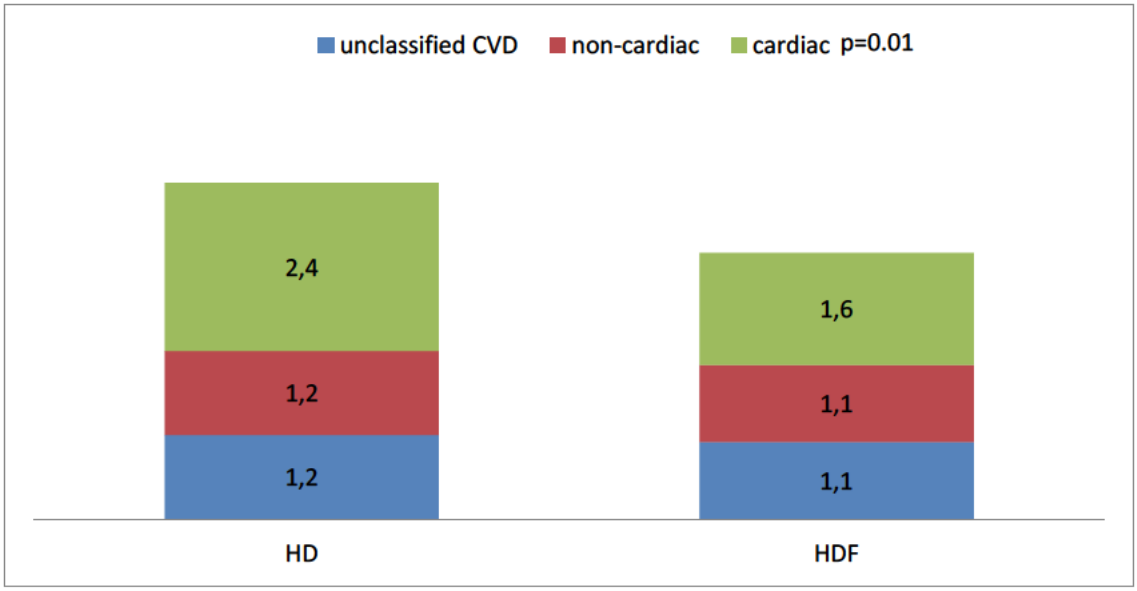
Values are n (%) for categorical variables, and mean (standard deviation) or median (Q1-Q3) for continuous variables. CVD, cardiovascular disease; BP, blood pressure; AVF, arteriovenous fistula; BMI, body mass index.

Table 2. Absolute number of deaths in the HD and online HDF groups and differences between groups; HR with 95% (CI) in the complete HDF cohort and in tertiles of the convection volume. The HD group is used as reference.

					Online HDF: BSA adjusted convection volume (L/session)			
	all	**HD**	**HDF**	**HD-HDF**	**Mean 22**	**<19**	**19-23**	**>23**
ALL CAUSES^	769	410	359	51	0.86 (0.75;0.99)	0.83 (0.66;1.03)	0.93(0.75;1.16)	0.78(0.62;0.98)
All CVD**	292	164	128	36	0.77 (0.61;0.97)	0.92(0.65;1.30)	0.71(0.49;1.03)	0.69(0.47;1.00)
Cardiac^	135	81	54	27	0.64(0.61;0.90)	0.95(0.65;1.39)	0.69(0.46;1.04)	0.70(0.47;1.05)
non-cardiac*	80	42	38	4	0.92(0.60;1.43)	0.64(0.26;1.55)	1.22(0.67;2.23)	0.86(0.47;1.78)
Unclassified^	77	41	36	5	0.90(0.58;1.42)	0.82(0.25;1.50	1.20(0.66;2.20)	0.85(0.46;1.55)
INFECTIONS*	150	77	73	4	0.94 (0.68;1.30)	1.50(0.92;2.46)	0.97(0.54;1.74)	0.62(0.32;1.19)
SUDDEN death^	112	56	56	0	0.99 (0.68;1.43)	1.09(0.69;1.74)	1.04(0.63;1.70)	0.69(0.39;1.20)
OTHER causes*	215	113	102	9	0.88 (0.68;1.13)	0.67(0.45;1.01)	1.13(0.77;1,67)	0.87(0.59;1.30)
*CVD including sudden death^*	*404*	220	184	36	*0.81 (0.65;1.00)*	*0.93(0.66;1.30)*	*0.82(0.59;1.14)*	*0.72(0.51;1.00)*

*HR: hazard rate, CI: confidence interval, BSA: body surface area, HD: hemodialysis, HDF: hemodiafiltration, CVD: cardiovascular disease. Cardiac CVD includes: myocardial infarction, arrhythmia and congestion; non-cardiac CVD includes: stroke, peripheral arterial disease; unclassified includes: CVD, but without any further specificity. (p for trend *= NS, ^=0.02-0.05, **=0.07) . Part of this table was published in (15).*

Figure 1: Annualized CVD mortality per 100 patient-years in the HD and online HDF groups.



The numbers in boxes represent fatal CVD events/100 patient years. The difference in fatal cardiac events between HD and HDF is significant (p=0.01)

Table 3. Annualized all cause and CVD mortality/100 patient years and NNT/year in the complete online HDF cohort and in tertiles of the convection volume. The HD group is used as reference.

	HD	Online HDF: BSA adjusted convection volume (L/session)			
	n.a.	Mean 22	<19	19-23	>23
All cause/100 PY	12.10	10.45	10.94	10.78	8.96
CVD/100 PY	4.84	3.73	4.28	3.66	3.51
NNT/year: overall/CVD	n.a.	61/90	86/178	75/84	32/75

HD: hemodialysis, HDF: hemodiafiltration, NNT: number needed to treat, BSA: body surface are, CVD: cardiovascular disease, PY: patient year

Table 4. Absolute number of cardiac deaths in the HD and online HDF groups and differences between groups; HR and 95% (CI) for pure cardiac CVD mortality. The HD group is used as reference

Cardiac cause	HD	HDF	HD - HDF	HR (95% CI)
MI, AR, congestion	86	54	32	0.64 (0.45;0.90)
MI, AR	53	30	23	0.58 (0.36;0.91)
MI	38	24	14	0.61 (0.37;1.02)

Adjusted for age, sex, albumin, creatinine, history of cardiovascular disease, history of diabetes. HD: hemodialysis, HDF: hemodiafiltration, MI: myocardial infarction, AR: arrhythmia.

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Authors' Contributions

MJN and MPCG drafted the report. SAEP did the analyses. All authors contributed to the interpretation of the data, the preparation of the manuscript, and the decision to submit for publication. MJN, MPCG, MLB and SAEP vouch for the validity of the study and are responsible for the integrity of the work as a whole.

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