Associations of hemodialysis dose and session length with mortality risk in Australian and New Zealand patients

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The optimal combination of hemodialysis (HD) dose and session length remains uncertain, and previous studies have not conclusively shown session length to be an important independent determinant of patient mortality. The objective of this study was to examine associations between HD dose and session length with mortality risk using data from the Australian and New Zealand Dialysis and Transplant Registry. Analyses were performed using a prospective inception cohort comprising all incident adult patients treated by thrice-weekly maintenance HD, who commenced renal replacement therapy with HD between 1 April 1997 and 31 March 2004. In all, 6593 patients were identified, of whom 4193 had sufficient data for multivariate analyses. HD dose (single pool fractional clearance of urea, *Kt/V*) and session length were included in analyses as those recorded 12 months after HD inception to reduce confounding by residual renal function. The outcome examined was patient mortality. Survival analyses included Kaplan–Meier calculations of survival and Cox regression for multivariate analyses. Covariates in Cox models included patient demographics, co-morbid medical conditions at HD inception, and HD operating parameters. After adjustment for covariates and each other, *Kt/V* of 1.30–1.39 and session length of 4.5–4.9 h were associated with the lowest mortality risk. There was no interaction between HD dose and session length. Thus, the optimal combination for mortality appears to be *Kt/V* of $\geqslant$1.3 and session length of $\geqslant$4.5 h. These data suggest a randomized controlled trial to test these hypotheses, and support the inclusion of criteria relating to session length in definitions of adequate HD practice.

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The annual mortality rate in hemodialysis (HD) populations is unacceptably high. In the United States (US), it remains consistently higher than that in other developed nations. It has been recently reported that approximately 30% of this increased mortality risk in the US compared to elsewhere is attributable to more severe co-morbid medical burden and older age.[1] The majority of this increased risk is therefore likely to result from HD practice patterns. There is in general a lack of critical evidence governing such practice, and adequate HD remains difficult to define and is to a large degree opinion-based. With such accessible and well-defined patients, there is an urgent need for further study to improve outcomes in this population.

The interrelated effects of HD dose and session length on patient outcomes have never been satisfactorily resolved. Interest in this area has remained high, especially after the publication of the Hemodialysis (HEMO) Study, which showed that outcomes were not improved with higher doses of dialysis than current consensus standards for patients receiving HD on a conventional short-hour thrice-weekly schedule.[2] One implication of this study is that further improvement in outcomes might necessarily involve more than simply change to dialysis operating parameters within the limitations of this particular schedule.[3] Increasingly, clinical outcomes research is focusing on unconventional HD regimens characterized by varying combinations of high and low efficiency, longer and shorter session length, and hemeral or nocturnal schedule. Simulations and limited clinical data have determined the impact of these different regimens upon solute control.[4–7] However, there is only limited information regarding clinical outcomes, with most series published out of single centers and none from large multi-center observational datasets.[4,5,8–10] There is even less known about the optimal HD session length for the thrice-weekly schedule, which is likely to remain the schedule for most HD patients unless studies of unconventional regimens yield conclusive results, and resources are made available to implement them.

The most conspicuous features of HD delivery in the US have historically been low HD dose and short session length.

Recent data indicate that HD dose is no longer disparate between the US and elsewhere, although HD sessions remain short.[11,12] In Australia and New Zealand, HD practice patterns have evolved independently of the fiscal regulations that have shaped corresponding practice in the US. There is greater variation in HD dose and session length in Australia and New Zealand, and this may allow for the identification of different associations between these parameters and patient outcomes. The objective of this study was to determine the association between both HD dose and session length with mortality risk in a large HD population receiving thrice-weekly treatments, using data from the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry.

RESULTS

Cohort description

In all, 6593 adult patients were identified as being treated with maintenance thrice-weekly HD (on HD both 90 days after commencement and also at 12 months after dialysis inception) in Australia and New Zealand between 1 April 1997 and 31 March 2004. Of these, 4171 patients had sufficient data to be included in modelling. Table 1 summarizes the characteristics of both cohorts. The study cohort was representative of the inception cohort except in two regards. The study cohort had a slightly lower proportion of patients whose primary renal disease was glomerulonephritis, and contained slightly older patients. Among the study cohort, there were 984 deaths recorded over 7228 person-years of follow-up. Of the deaths, 51% were attributed to cardiovascular disease, 12% to infections, and 13% to voluntary dialysis withdrawal.

Relationship between HD dose and session length

The distributions of HD dose and session length within the study cohort are shown in Figure 1. These parameters were not correlated ($r = 0.027$, $P = 0.08$). Figure 2 illustrates HD session length stratified by Kt/V for the study cohort. There was no evidence for an interaction between HD session length and Kt/V in any of the analyses, and each parameter was therefore analyzed separately.

HD dose

The most prevalent Kt/V category was $\geqslant 1.4$. Univariate and multivariate analyses are presented in Table 2. Hazard ratios derived from the final multivariate model are shown in Figure 3. Hemodialyser flux, body mass index, cerebrovascular disease and chronic lung disease were not found to be significant and independent covariates, and were therefore not included in the multivariate model. After adjustment for patient demographics and co-morbid conditions, Kt/V of 1.30–1.39 was associated with the lowest mortality risk. When further adjusted for HD session length, the relationship between mortality and dose persisted, suggesting that the mechanism for the lower mortality risk with higher Kt/V was not primarily longer session lengths. The fractional polynomial analyses (Figure 4) were similar to the categorical analysis.

Table 1 | Clinical characteristics of patients

Variable	Inception cohort (%)	Study cohort (%)
Number	6593	4171
Country		
Australia	5781 (87.7)	3700 (88.7)
New Zealand	812 (12.3)	471 (11.3)
Age (years) (median, IQR)	58.2 (46.2–68.7)	59.9 (48.3–70.7)[a]
Gender		
Male	4093 (62.1)	2570 (61.6)
Female	2500 (37.9)	1601 (38.4)
Race		
Caucasian/other	5133 (77.8)	3215 (77.9)
Aboriginal/Torres Islander	598 (9.1)	419 (10.0)
Asian	359 (5.5)	217 (5.2)
Maori/Pacific Islander	503 (7.6)	320 (7.7)
Late referral[b]	1600 (24.3)	1046 (25.1)
Smoking		
Current	929 (14.1)	568 (13.6)
Former	2712 (41.1)	1759 (42.2)
Diabetes mellitus		
Type 1	228 (3.5)	143 (3.4)
Type 2	2087 (31.7)	1442 (34.6)
Primary renal disease		
Glomerulonephritis	1967 (29.8)	1127 (27.0)[c]
Analgesic nephropathy	282 (4.3)	169 (4.1)
Hypertension/ischemic nephropathy	855 (13.0)	600 (14.4)
Polycystic kidney disease	509 (7.7)	279 (6.7)
Diabetic nephropathy	1701 (25.8)	1153 (27.6)
Other	1279 (19.4)	843 (20.2)
Coronary artery disease	2484 (37.7)	1646 (39.5)
Peripheral vascular disease	1659 (25.2)	1084 (26.0)
Cerebrovascular disease	898 (13.6)	594 (14.2)
Treated hypertension	5742 (87.1)	3620 (86.8)
Lung disease	968 (14.7)	631 (15.1)
BMI (kg/m^2) (median, IQR)	26.0 (22.8–30.1)	25.3 (22.4–29.0)[a]
Hemodialyser flux		
Low	5710 (86.6)	3465 (83.1)
High	883 (13.4)	706 (16.9)
Dialysis access[d]		
Arteriovenous fistula	3786 (77.4)	3223 (77.3)
Arteriovenous graft	706 (10.7)	589 (14.1)
Central venous catheter	456 (6.9)	359 (8.6)

BMI, body mass index; IQR, interquartile range.
[a]$P < 0.001$ and refer to the difference between the inception and study cohorts.
[b]Referral for nephrology pre dialysis care <3 months before dialysis inception.
[c]$P < 0.05$.
[d]There were 1645 missing responses.

HD session length

The most prevalent HD session length category was 4.0–4.4 h. Univariate and multivariate analyses are presented in Table 3. After adjustment for patient demographics and co-morbid medical conditions, session length of 4.5–4.9 h was associated

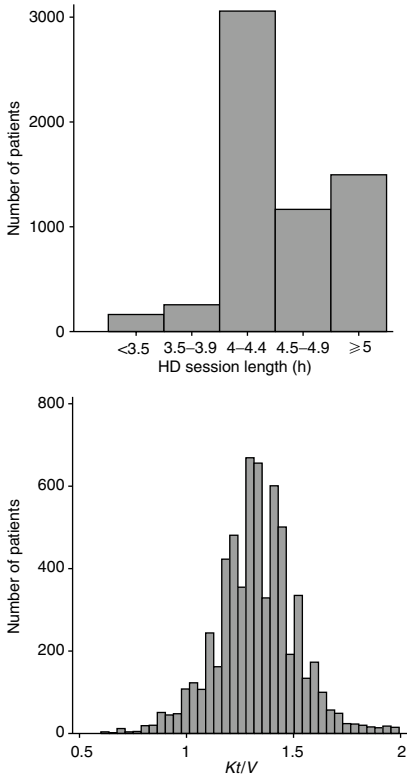

Figure 1 | Distribution of HD session length and dose within the study cohort.

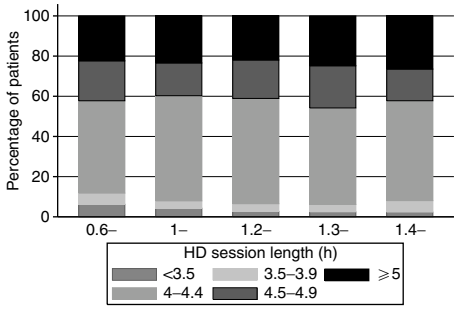

Figure 2 | Distribution of HD session length by categories of *Kt/V*.

with the lowest mortality risk, and <3.5 h the highest. When further adjusted for HD dose, the relationship between session length and mortality persisted, suggesting that the mechanism for the lower mortality risk with session length of 4.5–4.9 h was not primarily larger dose among HD patients receiving longer sessions. The fractional polynomial analyses (Figure 4) were similar to the categorical analysis; whether the mortality risk in the $\geqslant 5$ h group was further reduced could not be established due to insufficient power.

Characteristics of the study cohort for those treated with long ($\geqslant 4.5$ h) versus short (<4.5 h) sessions are presented in Table 4, and in general those receiving longer HD treatments were more likely to be larger, younger, male, current smokers, of Aboriginal, Maori, and Torres Strait and Pacific Island descent, and have diabetes mellitus. We specifically sought,

Table 2 | Mortality risk according to HD dose category

Model	HD dose *Kt/V* (*n*)	Hazard ratio (95% confidence intervals)
Univariate	<1.0 (161)	1.59 (0.17–2.17)[a]
	1.0–1.19 (705)	0.99 (0.81–1.20)
	1.20–1.29 (857)	1.00 (Ref)
	1.30–1.39 (1072)	0.79 (0.65–0.95)[b]
	⩾1.4 (1376)	0.92 (0.77–1.1)
Multivariate (excluding adjustment for HD session length)	<1.0 (161)	1.42 (1.03–1.96)[b]
	1.0–1.19 (705)	1.03 (0.84–1.25)
	1.20–1.29 (857)	1.00 (Ref)
	1.30–1.39 (1072)	0.79 (0.69–0.99)[a]
	⩾1.4 (1376)	1.42 (1.03–1.96)[b]
Adjusted for HD session length		
Univariate	<1.0 (161)	1.54 (1.13–2.11)[a]
	1.0–1.19 (705)	0.97 (0.79–1.18)
	1.20–1.29 (857)	1.00 (Ref)
	1.30–1.39 (1072)	0.79 (0.66–0.96)[c]
	⩾1.4 (1376)	0.89 (0.75–1.06)
Multivariate	<1.0 (161)	1.42 (1.03–1.97)[a]
	1.0–1.19 (705)	1.03 (0.84–1.25)
	1.20–1.29 (857)	1.00 (Ref)
	1.30–1.39 (1072)	0.79 (0.65–0.95)[c]
	⩾1.4 (1376)	0.83 (0.69–0.99)[c]

HD, hemodialysis.
[a]$P<0.01$.
[b]$P<0.001$.
[c]$P<0.05$.

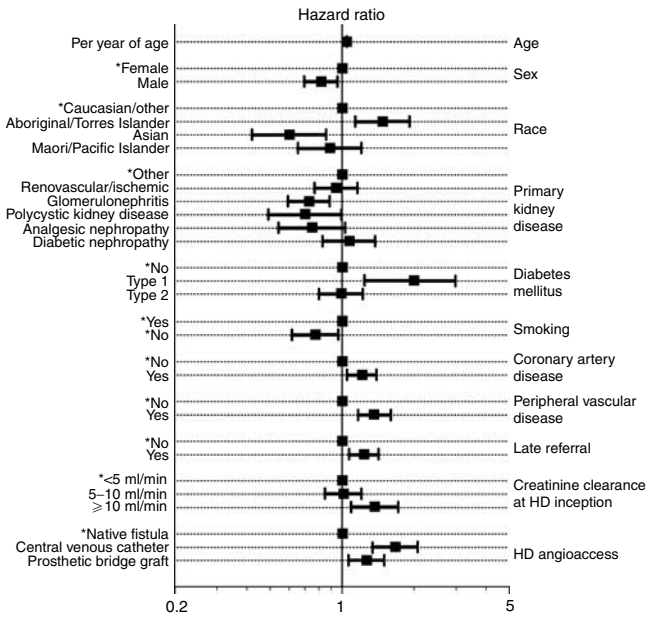

Figure 3 | Hazard ratios for mortality within study cohort according to selected predictive variables. Hazard ratios were derived within a multivariate Cox proportional-hazard model, with shared frailty for each treatment centre. Asterisks indicate the reference categories. Horizontal bars indicate 95% confidence intervals.

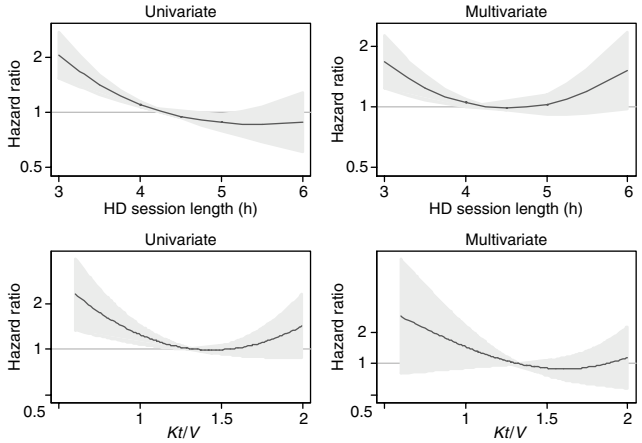

Figure 4 | Univariate and multivariate fractional polynomial graphs depicting the relationship between both HD session length and dose with mortality risk. The multivariate graphs are fully adjusted for patient demographic and co-morbid medical conditions, and HD session length and dose in the other's respective analyses. Shaded areas indicate 95% confidence intervals.

Table 3 | Mortality risk according to HD session length category

Model	HD session length in hours (*n*)	Hazard ratio (95% confidence intervals)
Univariate	<3.5 (121)	1.75 (1.27–2.40)[a]
	3.5–3.9 (187)	1.18 (0.88–1.60)
	4–4.4 (2091)	1.00 (Ref)
	4.5–4.9 (753)	0.71 (0.59–0.86)[a]
	⩾5 (1019)	0.72 (0.60–0.86)[a]
Multivariate (excluding adjustment for *Kt/V*)	<3.5 (121)	1.69 (1.23–2.32)[b]
	3.5–3.9 (187)	1.11 (0.83–1.48)
	4–4.4 (2091)	1.00 (Ref)
	4.5–4.9 (753)	0.79 (0.65–0.96)[c]
	⩾5 (1019)	0.99 (0.82–1.18)
Adjusted for HD dose		
Univariate	<3.5 (121)	1.67 (1.22–2.31)[b]
	3.5–3.9 (187)	1.19 (0.88–1.60)
	4–4.4 (2091)	1.00 (Ref)
	4.5–4.9 (753)	0.71 (0.59–0.85)[a]
	⩾5 (1019)	0.71 (0.59–0.86)[a]
Multivariate	<3.5 (121)	1.57 (1.14–2.17)[b]
	3.5–3.9 (187)	1.09 (0.81–1.46)
	4–4.4 (2091)	1.00 (Ref)
	4.5–4.9 (753)	0.80 (0.66–0.97)[c]
	⩾5 (1019)	1.02 (0.85–1.22)

HD, hemodialysis.
[a]$P<0.001$.
[b]$P<0.01$.
[c]$P<0.05$.

Table 4 | Clinical characteristics of the study cohort compared by HD session length category

Variable	<4.5 h (%)	⩾4.5 h (%)
Number	2399	1722
Country		
Australia	2191 (91.3)	1509 (85.2)[a]
New Zealand	208 (8.7)	263 (14.8)
Age (years) (median, IQR)	65.4 (53.2–73.6)	58.1 (47.1–68.2)[a]
Gender		
Male	1299 (54.1)	1271 (71.7)[a]
Female	1100 (45.9)	501 (28.3)
Race		
Caucasian/other	1999 (83.3)	1216 (68.6)[a]
Aboriginal/Torres Islander	152 (6.3)	267 (15.1)
Asian	137 (5.7)	80 (4.5)
Maori/Pacific Islander	111 (4.6)	209 (11.8)
Late referral[b]	566 (23.6)	480 (27.1)[c]
Smoking		
Current	301 (12.6)	267 (15.1)[a]
Former	976 (40.7)	783 (44.2)
Diabetes mellitus		
Type 1	87 (3.6)	56 (3.2)[a]
Type 2	699 (29.1)	742 (41.9)
Primary renal disease		
Glomerulonephritis	623 (26.0)	504 (28.4)[a]
Analgesic nephropathy	119 (5.0)	50 (2.8)
Hypertension/ischemic nephropathy	412 (17.2)	188 (10.6)
Polycystic kidney disease	155 (6.5)	124 (7.0)
Diabetic nephropathy	562 (23.4)	591 (33.4)
Other	528 (22.0)	315 (17.8)
Coronary artery disease	979 (40.8)	667 (37.6)[c]
Peripheral vascular disease	617 (25.7)	467 (26.4)
Cerebrovascular disease	343 (14.3)	251 (14.2)
Treated hypertension	2399 (85.9)	1559 (87.9)
Lung disease	363 (15.1)	268 (15.1)
BMI (kg/m^2) (median, IQR)	24.9 (22.0–28.6)	27.8 (24.2–32.4)[a]
Hemodialyser flux		
Low	2030 (84.6)	1435 (81.0)[d]
High	369 (15.4)	337 (19.0)
Dialysis access[e]		
Arteriovenous fistula	1832 (76.4)	1391 (78.5)[d]
Arteriovenous graft	332 (13.8)	257 (14.5)
Central venous catheter	235 (9.8)	124 (7.0)

BMI, body mass index; IQR, interquartile range.
[a]$P<0.001$ and refer to the difference between the subgroups receiving longer and shorter HD treatments.
[b]Referral for nephrology pre dialysis care <3 months before dialysis inception.
[c]$P<0.05$.
[d]$P<0.01$.
[e]There were 1645 missing responses.

but could not formally demonstrate, a statistical interaction between session length and body mass index (BMI) in the final regression model (interaction HD session length × BMI $P=0.22$). The issue was further explored by creating categories allowing comparisons of all combinations of BMI categories and session length in the multivariate model (Figure 5). Examined in this manner, the association of longer HD sessions with reduced mortality was seen among those in middle and higher BMI groups, but not in the lowest BMI group.

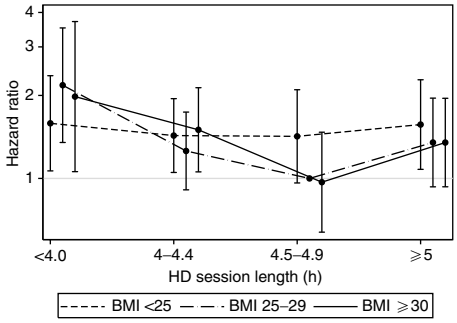

Figure 5 | Hazard ratios (HR) for mortality by HD session length and body mass index (BMI). The multivariate analyses are fully adjusted using the final regression model. All HR are relative to the group with BMI 25–29 and session length 4.5–4.9 h. Mortality risk is the same for different session lengths in group with BMI <25 ($P=0.85$), although differences are more likely in the groups with BMI 25–29 ($P=0.01$) and $\geqslant 30$ ($P=0.06$). Error bars indicate 95% confidence intervals.

DISCUSSION

It seems axiomatic that more dialysis should provide better outcomes, and there are few who would consider uremic toxicity to be abrogated by the current standard of short-hour thrice-weekly HD. However, optimal HD practice does remain uncertain. There is expert consensus about HD dose in the Kidney Disease Outcomes Quality Initiative and European Best Practice Guidelines,[13,14] and also in the Caring for Australians with Renal Impairment guidelines under development for Australian and New Zealand chronic kidney disease patients (www.kidney.org.au/cari). In contrast, there is no such consensus about HD session length. The recommendations of the Caring for Australians with Renal Impairment guidelines for well-powered, statistically robust observational analyses have led to these analyses of the ANZDATA Registry.

The findings of this study support the minimum standards for HD dose advocated by the aforementioned consensus guidelines. However, the crucial finding in this study was that shorter HD session length was associated with higher mortality risk, independently of HD dose. This implies that the evaluation of dialysis adequacy by HD dose alone may be insufficient to optimize outcomes, and that adequate dialysis may be characterized by HD session length of 4.5 h or longer, irrespective of dose. This paradigm has enormous implications for both HD providers and patients.

The relative effects of HD dose and session length on patient outcomes were originally explored in the National Cooperative Dialysis Study.[15] This study showed that small solute control was a more important determinant of patient morbidity than HD session length. The study did in fact suggest a causal relationship between shorter dialysis and excess patient morbidity, although it was not sufficiently different from chance ($P=0.056$) to be regarded as significant. As a result, HD session length has often not been considered by both researchers and clinicians in the endeavor to define and deliver adequate dialysis.

To our knowledge, there have been no studies other than the National Cooperative Dialysis Study that have addressed the issue of HD dose and session length in a definitive manner. However, a number of observational studies have provided support for both dose and length as determinants of patient mortality. Single-center experience from Tassin, France has shown superior surrogate and actual patient outcomes with longer HD session lengths.[16,17] The most compelling multi-center observations have been made using registry-sourced data from a 1993 Japanese cohort, in which HD session length of 5.0–5.5 h was shown to be independently associated with the lowest mortality risk ($P<0.01$), even when analyses were adjusted for Kt/V.[18] Observations more applicable to US and European populations have been made using US patient cohorts from the 1980s, including two studies in which HD session length shorter than 3.5 h was independently associated with up to approximately doubled mortality risk compared to longer sessions, although neither analysis was adjusted for HD dose.[19,20] Most recently, the Dialysis Outcome and Practice Patterns Study has presented various analyses using a large cohort of Japanese, US and European patients, in which HD session length shorter than 3.5 h was shown to be independently associated with a 33% higher mortality risk ($P=0.004$), even when analyses were adjusted for Kt/V.[21]

The data from this study confirm that HD delivery in Australia and New Zealand is characterized by relatively high delivered HD dose, achieved by longer HD treatments rather than higher blood flow rates. HD session length averaged 263 min and blood flow rate 294 ml/min, as compared with 213 min and 401 ml/min in the US and 234 min and 296 ml/min in Europe.[12,22] This HD practice pattern can be attributed to two factors particular to Australia and New Zealand. Firstly, the higher prevalence of home hemodialysis in Australia and New Zealand (stable at approximately 14 and 25% of HD patients, respectively[23]) may potentially dilute the effect of scheduling restraints within facilities that so often lead to shortening of hours. Secondly, the prevailing opinion among nephrologists in Australia and New Zealand is that HD session length is at least as, if not more, important than dose: many centers do not prescribe HD treatments of less than 5 h, and those dialyzing their patients for longer hours often do not measure HD dose.

There are several possible mechanisms for improved outcomes with longer sessions. Importantly, our analyses have confirmed that the effect of longer HD session length on mortality in this study was not as a result of statistical confounding by BMI. If anything, the effect of session length is more marked among those with higher BMI. Other studies have shown that longer HD sessions result in greater removal of larger molecules,[7] and improved phosphate and bicarbonate control,[24] even for a given amount of small solute removal.[25–27] In addition, less intradialytic hemodynamic instability allows more consistent achievement of dry weight, better blood pressure control, and probably less sympathetic hyperactivity.[28,29] Despite these findings, it is important to

note that both left ventricular hypertrophy and dialysis-related amyloidosis still affect patients receiving longer thrice-weekly HD treatments,[30,31] which makes the case for these regimens less intuitive and in need of corroboration by clinical study. Figure 5 suggests that the mechanisms for improved outcomes with longer sessions may be ameliorated by smaller body size, although it is unclear in our study as to whether low BMI was a proxy for malnutrition, inflammation, or Asian race. The mechanisms responsible for the relationship between HD session length and mortality risk demonstrated in this study are impossible to infer from the ANZDATA Registry. Like most registries, the advantages of broad-based national-level data are offset by a lack of detail.

A major strength of this study is its external validity. Studies from around the world analyze populations with often quite different characteristics. The cohort in this study has differences but also important similarities to North American and European hemodialysis populations.[32,33] The Dialysis Outcome and Practice Patterns Study allows for pertinent comparisons, and Table 5 shows the clinical characteristics of the North American and European Dialysis Outcome and Practice Patterns Study cohorts flanking the period of observation in this study. Of course, differences between dialysis populations do not preclude generalization of study findings from one to another. For instance, external validity of this study will only be compromised if the effect of HD dose or session length on mortality is modified in any way by the characteristics that differ between dialysis populations. Other investigators have formally demonstrated an interaction between HD dose and both gender and race,[34,35] but not for other variables such as angioaccess type, etc. The findings in this study pertaining to HD dose should therefore be generalized cautiously to populations with different proportions of females and black patients. In contrast, the findings pertaining to HD session length are reasonably able to be generalized to other patient populations, more so perhaps than the previously discussed data from the Japanese national registry which are regarded by some opinion leaders to have poor external validity.[36]

Limitations of this research pertain to study design and data source. Although ANZDATA Registry data are collected prospectively, the study design is retrospective and observational, using an inception cohort that by definition restricts analyses to patients who have survived at least a year on dialysis using those parameters that have been collected. Although associations do not prove causality, observational research can still contribute potentially important and beneficial knowledge. Patients numbers are large, and are not limited to those who fulfil the given inclusion criteria. These issues are particularly relevant, as major interventional trials in this area have been criticized for both sample size and selection.[37,38] Moreover, a greater number of individual HD operating parameters may be examined in observational survival studies, since their analyses within interventional trials will be limited by the study protocol. Observational studies are therefore useful to develop hypotheses for survival analyses, and shape both the design and interpretation of randomized controlled interventional trials that can be used to definitely prove causality.

Statistical adjustments in this study minimize the confounding effects of measured co-variates on the relationship between HD session length and mortality risk. However, it is possible that there is still residual confounding from non-randomized assignment of patients to different HD dose and session lengths. The use of a shared frailty model explicitly accounts for 'center effects'; this technique is the survival analog of a 'random effects' model and gives more conservative outcomes than other approaches.

The data source for these analyses was a registry, and as a consequence potentially important variables have been omitted from our analyses since they are not collected by the ANZDATA Registry. These include serum chemistries such as phosphate, calcium, albumin, and also clinical parameters such as functional status, measured residual renal function, and left ventricular structure/function. There is also potential for misclassification of patient co-morbid conditions, since these are based on the opinion of the treating nephrologist without the benefit of rigorous or standardized criteria. Finally, standard blood sampling techniques for Kt/V are recommended by the ANZDATA Registry, but no audit has been conducted to determine compliance. Variability in technique may therefore result in measurement

Table 5 | Clinical characteristics of the United States and European hemodialysis cohorts from the DOPPS

	United States–DOPPS		Europe–DOPPS	
	Phase 1 (1998)	Phase 2 (2002/2003)	Phase 1 (1998)	Phase 2 (2002/2003)
n	12 126	7028	6109	7313
Mean age (years)	59.5	61.6	60.4	62.9
Male (%)	53	54	57	58
Black (%)	41	34	2	2
Diabetes mellitus as primary cause of end-stage renal failure (%)	41	48	16	20
Diabetes mellitus (%)	46	53	20	24
Arteriovenous fistula (%)	24	31	80	79

All statistics shown are based upon prevalent cross-sections; Europe–DOPPS for this analysis was comprised of the five European countries participating in both phases of DOPPS, and these countries were France, Germany, Italy, Spain, and the United Kingdom (personal communication RL Pisoni, 13 August 2005).
DOPPS, Dialysis Outcomes and Practice Patterns Study.

error for *Kt/V*, the impact of which is difficult to estimate in this study.

The findings of this study suggest a randomized controlled trial to test the influence of HD session duration. The primary intervention should be randomization for HD session length of 4.0–4.5 h (hazard ratio 1.0) vs 4.5–5.0 h (hazard ratio 0.8), with HD dose to be controlled in either arm such that *Kt/V* is greater than 1.3. The utilization of a two-by-two factorial design with a second intervention of randomization for HD dose is probably not justified on the basis of the HEMO study. The mortality rate of 9% per year for our study cohort indicates that a proposed trial would be of 4 years duration (2 years recruitment and 2 years follow-up), and that a large sample size of 1757 patients would be needed to demonstrate a 25% mortality difference with the primary intervention of HD session length.

In conclusion, this study demonstrates that both HD dose and session length are independently associated with mortality risk in Australia and New Zealand patient populations. This supports the direction of recent and proposed research involving the prospective study of patient outcomes with alternative HD schedules.

MATERIALS AND METHODS

Study population

The ANZDATA Registry collects data on all patients with end-stage renal disease in Australia and New Zealand. Data collection rounds occur at 6-monthly intervals, at 31 March and 30 September of each year. End-stage renal disease patients are defined as those with a diagnosis of chronic renal failure and for whom renal replacement therapy is intended to be an indefinite treatment. Details of the structure and methods of the registry have been reported elsewhere.[23] The data collected include information about the underlying primary renal disease, pre-dialysis care, demographic details, presence of co-morbid medical conditions as indicated by the treating nephrologist (type I and II diabetes mellitus, coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, treated hypertension, current and former smoking), and the type and details of renal replacement therapy including angioaccess. Data about HD dose have only been included since the April 1997 survey. An inception cohort was created by identifying all incident end-stage renal disease patients age 25 years or older at commencement of dialysis, treated by thrice-weekly maintenance HD (on HD both 90 days after commencement and also at 12 months after dialysis inception) in Australia and New Zealand between 1 April 1997 and 31 March 2004. Patients were excluded if they died or changed renal replacement modality within 12 months of HD inception.

Statistical analyses

Follow-up for analysis commenced 12 months after commencement of renal replacement therapy. HD dose and session length were included in analyses as that first recorded 12 months after dialysis inception to minimize confounding from residual renal function. HD dose was expressed as single-pool fractional clearance of body water for urea (*Kt/V*);[39] values reported as URR to the ANZDATA Registry were converted to *Kt/V* by method of Casino and Basile.[40] Patients with reported or calculated *Kt/V* of less than 0.6 or greater than 2.4 were excluded from analyses as likely erroneous data. Primary analysis of *Kt/V* and session length was performed by categories. As these parameters are continuous variables, they were also modelled as fractional polynomial functions.[41,42] This technique allows for the fitting of a smooth line or curve without the artifacts observed with cubic splines, and avoids the problems associated with arbitrary selection of categories.[43,44]

Observational data are presented as median (interquartile range) or number (percentage). Where necessary, comparisons between groups were made using the Mann–Whitney *U*-test for continuous variables, and the χ^2 test for categorical ones.

The outcome examined was patient mortality, based upon details provided by the treating unit. HD treatment was censored at the time of transplantation. Survival analyses included Kaplan–Meier calculations of survival and Cox regression for multivariate analyses. Cox models were stratified by year of dialysis commencement. The covariates included in the Cox models were age, gender, race, primary renal disease, calculated creatinine clearance at dialysis inception,[45] late referral for nephrology pre-dialysis care (<3 months before commencement of renal replacement therapy), type I and II diabetes mellitus, and presence of the above co-morbid conditions at commencement of dialysis. For reported co-morbidities, 'suspected' was included with 'yes' for analyses. Angioaccess type (native fistula, prosthetic bridge graft, tunnelled and untunnelled central venous catheter) and hemodialyzer flux were included in analyses as that first recorded as being in use 12 months after dialysis inception. BMI was modelled as a categorical variable (<20, 20–24.9, 25–29.9, and $>30\,kg/m^2$) using recorded height at, and weight 12 months after, dialysis inception. Hemoglobin was not included in analyses since these data have only been collected since 1 October 2000. Hemodialyzer reuse also was not included as this practice is extremely rare in Australia and New Zealand. Follow-up was determined to 31 March 2004. Multivariate models initially included all of the covariates; those with $P>0.05$ were dropped in a backward stepwise manner. All models included a gamma-distributed shared frailty, using the hospital of initial treatment as the group. Potential interactions were sought using likelihood ratio tests.

Statistical significance was attributed to findings if the two-tailed *P*-value was <0.05. All analyses were undertaken using Intercooled Stata 8.2 (StataCorp, College Station, TX, USA).

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REFERENCES

1. Goodkin D, Bragg-Gresham J, Koenig K *et al.* Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; **14**: 3270–3277.
2. Eknoyan G, Beck GJ, Cheung AK *et al.* Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002; **347**: 2010–2019.
3. Henderson LW. The inadequacy of Kt/V_{urea}: a brief history of time. *Hemodial Int* 2004; **8**: 139–143.
4. Kooistra M, Vos J, Koomans H *et al.* Daily home haemodialysis in The Netherlands: effects on metabolic control, haemodynamics, and quality of life. *Nephrol Dial Transplant* 1998; **13**: 2853–2860.
5. Woods J, Port F, Orzol S *et al.* Clinical and biochemical correlates of starting 'daily' hemodialysis. *Kidney Int* 1999; **55**: 2467–2476.

6. Raj D, Ouwendyk M, Francoeur R *et al.* Beta(2)-microglobulin kinetics in nocturnal haemodialysis. *Nephrol Dial Transplant* 2000; **15**: 58–64.
7. Goldfarb-Rumyantzev A, Cheung A, Leypoldt JK. Computer simulation of small-solute and middle-molecule removal during short daily and long thrice-weekly hemodialysis. *Am J Kidney Dis* 2002; **40**: 1211–1218.
8. Williams A, Chebrolu S, Ing T *et al.* Early clinical, quality-of-life, and biochemical changes of 'daily hemodialysis' (6 dialyses per week). *Am J Kidney Dis* 2004; **43**: 90–102.
9. Pierratos A. Daily nocturnal home hemodialysis. *Kidney Int* 2004; **65**: 1975–1986.
10. Andre M, Rembold S, Pereira C *et al.* Prospective evaluation of an in-center daily hemodialysis program: results of two years of treatment. *Am J Nephrol* 2002; **22**: 473–479.
11. Port F, Pisoni R, Bragg-Gresham J *et al.* DOPPS estimates of patient life years attributable to modifiable hemodialysis treatment practices in the United States. *Blood Purif* 2004; **22**: 175–180.
12. Goodkin D, Young E. An update on the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Contemp Dial Nephrol* 2001; **22**: 36–40.
13. National Kidney Foundation. K/DOQI Clincal Practice Guidelines for Hemodialysis Adequacy, 2000. *Am J Kidney Dis* 2001; **37**(Suppl 1): S7–S64.
14. European Dialysis and Transplant Association – European Renal Association. European best practice guidelines for haemodialysis. *Nephrol Dial Transplant* 2002; **17**(Suppl 7): 17–31.
15. Lowrie E, Laird N, Parker T *et al.* Effect of dialysis prescription on patient morbidity. *N Engl J Med* 1981; **305**: 1176–1180.
16. Innes A, Charra B, Burden R *et al.* The effect of long, slow haemodialysis on patient survival. *Nephrol Dial Transplant* 1999; **14**: 919–922.
17. Charra B, Hurot J-M, Chazot C *et al.* Comparison of survival data. *Kidney Int* 2000; **58**: 901–902.
18. Shinzato T, Nakai S, Akiba T *et al.* Survival in long-term haemodialysis patients: results from the annual survey of the Japanese Society for Dialysis Therapy. *Nephrol Dial Transplant* 1997; **12**: 884–888.
19. Held P, Levin N, Bovbjerg R *et al.* Mortality and duration of hemodialysis treatment. *JAMA* 1991; **265**: 871–875.
20. Lowrie EG, Lew NL. Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 1990; **15**: 458–482.
21. Saran R, Bragg-Gresham C, Coombe V *et al.* High ultrafiltration rates are associated with poor outcomes in hemodialysis patients: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; **14**: 234A.
22. Hecking E, Bragg-Gresham J, Rayner H *et al.* Haemodialysis prescription, adherence and nutritional indicators in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2003; **19**: 100–107.
23. Russ G. *ANZDATA Registry Report 2003*. Australia and New Zealand Dialysis and Transplant Registry: Adelaide, Australia, 2003.
24. Charra B, Chazot C, Jean G *et al.* Long, slow dialysis. *Miner Eletcrolyte Metb* 1999; **25**: 391–396.
25. Mactier R, Madi A, Allam B. Comparison of high-efficiency and standard haemodialysis providing equal urea clearances by partial and total dialysate quantification. *Nephrol Dial Transplant* 1997; **12**: 1182–1186.
26. Johnsson E, Attman P, Samuelsson O *et al.* Improved clearance of iohexol with longer haemodialysis despite similar *Kt/V* for urea. *Nephrol Dial Transplant* 1999; **14**: 2407–2412.
27. Vaithilingam I, Polkinghorne K, Atkins R *et al.* Time and exercise improve phosphate removal in hemodialysis patients. *Am J Kidney Dis* 2004; **43**: 85–89.
28. Charra B, Calemard M, Laurent G. Importance of treatment time and blood pressure control in achieving long-term survival on dialysis. *Am J Nephrol* 1996; **16**: 35–44.
29. McGregor D, Buttimore A, Lynn K *et al.* A comparative study of blood pressure control with short in-center versus long home hemodialysis. *Blood Purif* 2001; **19**: 293–300.
30. McGregor D, Buttimore A, Nicholls M *et al.* Ambulatory blood pressure monitoring in patients receiving long, slow home haemodialysis. *Nephrol Dial Transplant* 1999; **14**: 2676–2679.
31. Laurent G, Calemard M, Charra B. Dialysis related amyloidosis. *Kidney Int* 1988; **24**: S32–S34.
32. U.S. Renal Data System. *USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2003.
33. ERA-EDTA Registry. *ERA-EDTA Registry 2003 Annual Report*. Academic Medical Center: Amsterdam, The Netherlands, 2005.
34. Port F, Wolfe R, Tempie E *et al.* High dialysis dose is associated with lower mortality among women but not among men. *Am J Kidney Dis* 2004; **43**: 1014–1023.
35. Depner T, Daugirdas J, Greene T *et al.* Dialysis dose and the effect of gender and body size on outcome in the HEMO Study. *Kidney Int* 2004; **65**: 1386–1394.
36. Friedman E. International comparisons of survival on dialysis: are they reliable? *Hemodial Int* 2003; **7**: 59–66.
37. Locatelli F. Dose of dialysis, convection and haemodialysis patients outcome – what the HEMO study doesn't tell us: the European viewpoint. *Nephrol Dial Transplant* 2003; **18**: 1061–1065.
38. Depner T, Gotch F, Port F *et al.* How will the results of the HEMO study impact dialysis practice? *Semin Dial* 2003; **16**: 8–21.
39. Gotch F. Kinetic modeling in hemodialysis. In: Nissensen A, Gentile D, Fine R (eds). *Clinical Dialysis*. 2nd edn. East Norwalk, Connecticut: Appleton and Lange, 1989, pp 118–146.
40. Basile C, Casino F, Lopez T. Percent reduction in blood urea concentration during dialysis estimates *Kt/V* in a simple and accurate way. *Am J Kidney Dis* 1990; **15**: 40–45.
41. Royston P. A strategy for modelling the effect of a continuous covariable in medicine and epidemiology. *Stat Med* 2000; **19**: 1831–1847.
42. Sauerbrei W, Royston P. Building multivariable prognostic and diagnostic models: transformation of the predictors using fractional polynomials. *J R Stat Soc A* 1999; **162**: 71–94.
43. Greenland S. Dose–response and trend analysis in epidemiology: alternatives to categorical analysis. *Epidemiology* 1995; **6**: 356–365.
44. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 1999; **28**: 964–974.
45. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.