Patient survival on haemodiafiltration and haemodialysis: a cohort study using the Australia and New Zealand Dialysis and Transplant Registry

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ABSTRACT

Background: It is unclear if haemodiafiltration improves patient survival compared to standard haemodialysis. Observational studies have tended to show benefit with haemodiafiltration, while meta-analyses have not provided definitive proof of superiority.

Methods: Using data from the ANZDATA Registry, this binational inception cohort study compared all adult patients who commenced haemodialysis in Australia and New Zealand between 2000 and 2014. The primary outcome was all-cause mortality. Cardiovascular mortality was the secondary outcome. Outcomes were measured from the first haemodialysis treatment and were examined using multivariable Cox regression analyses. Patients were censored at permanent discontinuation of haemodialysis or at 31 December 2014. Analyses were stratified by country.

Results: The study included 26,961 patients (4,110 haemodiafiltration, 22,851 standard haemodialysis; 22,774 Australia, 4,187 New Zealand) with a median follow-up of 5.31 (IQR 2.87-8.36) years. Median age was 62 years, 61% were male, 71% were Caucasian. Compared to standard haemodialysis, haemodiafiltration was associated with a significantly lower risk of all-cause mortality (adjusted HR for Australia 0.79, 95% CI 0.72-0.87; adjusted HR for New Zealand 0.88, 95% CI 0.78-1.00). In Australian patients, there was also an association between haemodiafiltration and reduced cardiovascular mortality (adjusted HR 0.78, 95% CI 0.64-0.95).

Conclusions: Haemodiafiltration was associated with superior survival across patient subgroups of age, sex and comorbidity.

Keywords: dialysis; end stage renal disease; hemodiafiltration; hemodialysis; survival.

INTRODUCTION

Despite gradual improvements in patient survival on haemodialysis, annual crude mortality rates remain high, ranging from 6.6% in Japan to 21.7% in the United States.[1,2] While increasing patient age and comorbidity burden are key contributors to the heightened risk of death, the cardiovascular sequelae of intradialytic haemodynamic instability and uraemic toxin accumulation may also play a role.[3–5]

Through mitigation of intradialytic hypotension and enhanced removal of medium and large uraemic toxins, it has been hypothesised that use of haemodiafiltration may confer a survival benefit compared to standard haemodialysis. Several observational studies have supported an association between haemodiafiltration and reduced all-cause and cardiovascular mortality,[6–13] although a recent analysis using data from European countries participating in the Dialysis Outcomes and Practice Patterns Study did not detect a survival difference between modalities.[14] Four meta-analyses[15–18] have not conclusively supported the superiority of haemodiafiltration. The most consistent finding has been that of an association between high convection volume haemodiafiltration and superior survival, from secondary, post-hoc, and pooled individual patient data analyses of the randomised trials.[13,19–22] Although encouraging, such analyses can only be interpreted as observational, since convection volume was not randomised within the studies.

Existing observational studies have been limited by single centre design, small patient numbers, inclusion of prevalent haemodialysis patients, or variable haemodiafiltration practices. Randomised trials have been weakened by flawed methodology, failure to achieve or adequately dose convection volume, and insufficient duration and completeness of follow

up. No large study has compared haemodiafiltration and standard haemodialysis outside Europe, and regional practice pattern variation may be significant.[23] In light of these limitations, this study used a population-based approach to compare patient survival on haemodiafiltration and standard haemodialysis in Australia and New Zealand over a 15 year period.

METHODS

Study design

This was an inception cohort study using patient records from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry. The ANZDATA Registry collects data annually from all units throughout Australia and New Zealand for all people receiving chronic renal replacement therapy. Details of the ANZDATA Registry have been previously described.[24]

Study population

All adult patients (≥ 18 years) who commenced standard haemodialysis or haemodiafiltration in Australia or New Zealand between 1 January 2000 and 31 December 2014 were included in the study, including those who had previously received peritoneal dialysis or a renal transplant. Patients were censored at the time of permanent discontinuation of haemodialysis (i.e. transfer to peritoneal dialysis, renal transplantation, recovery of renal function, or loss to follow up) or at 31 December 2014. Patients who temporarily discontinued haemodialysis (i.e. renal transplantation or peritoneal dialysis with return to haemodialysis) were removed from the risk set but were re-included from the time they re-initiated haemodialysis.

Data collection

ANZDATA records were used for patient demographics (age, sex, race, country), comorbidities (body mass index, chronic lung disease, coronary artery disease,

cerebrovascular disease, peripheral vascular disease, diabetes mellitus, smoking status), and dialysis prescription at the commencement of haemodialysis (vascular access type, blood flow rate, treatment time, setting [home, hospital, satellite], erythropoietin use). The initial mode of haemodialysis was determined at 90 days after the first treatment. The haemodiafiltration group included all patients who received at least one haemodiafiltration treatment during the study period. The ANZDATA Registry updates haemodialysis modality (haemodiafiltration or haemodialysis) and prescription (treatment time, blood flow rate, vascular access) annually; changes in renal replacement therapy modality (haemodialysis, peritoneal dialysis or transplant) and setting (hospital, satellite, or home) are updated in real time.

Derived indices included Socio-Economic Indexes For Areas (SEIFA), Accessibility/Remoteness Index of Australia Plus (ARIA+) scores, and estimated haemodiafiltration convection volume. SEIFA and ARIA+ scores were developed by the Australian Bureau of Statistics and use postcodes to estimate socioeconomic status and residential remoteness. A SEIFA score in the highest decile was considered advantaged, whereas a score in the lowest decile was used to describe socioeconomic disadvantage. ARIA+ categories were recorded as 0 to <1 major city, 1 to <3 regional, 3 to 4 remote. SEIFA and ARIA scores were calculable for Australian patients only. There is no equivalent measure calculable for New Zealand patients. Estimates of minimum delivered haemodiafiltration convection volume were derived by multiplying blood flow rate, dialysis hours, and a minimum filtration fraction of 0.20, assuming postdilution haemodiafiltration mode.

Clinical outcomes

The primary outcome was all-cause mortality, measured as the time from the first haemodialysis treatment to death. Cause-specific mortality was estimated using cause of death reported to ANZDATA. Time to cardiovascular death (i.e. death due to myocardial ischaemia, cardiac failure, cardiac arrest, pulmonary oedema, or hyperkalaemia) was a secondary outcome.

Statistical analyses

All data were analysed using STATA software package (version 14.0, College Station, TX: StataCorp LP, USA). All reporting was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[25]

Baseline characteristics were expressed as patient numbers (n, %), means (± standard deviation), or medians (interquartile range, IQR), as appropriate. Univariable and multivariable Cox regression models were used to examine the primary outcome, overall mortality. Because the ANZDATA Registry records modality changes, haemodialysis modality was treated as a time-varying covariate, where patients could switch from one modality to the other. Multivariable models included all variables with a univariable p-value less than 0.25. Interaction terms between haemodiafiltration and pre-specified variables (age, sex, race, body mass index, and year of haemodialysis start) were examined. Backwards elimination was used to exclude variables or interaction terms that were not confounders (a confounder was defined as >10% change in hazard ratio [HR] for haemodiafiltration), or those that were not statistically significant. Statistically significant was defined as a p-value <0.05 for main effects and p <0.01 for effect modifiers. Standard errors were adjusted for the

clustering of observations within treatment centres using the sandwich estimator.[26] To ensure comparability between the Australian and New Zealand analyses, all variables remaining in either the Australian or New Zealand models were included in the final multivariable models. Modelled survival curves were generated for each country. To test for any cumulative effect of haemodiafiltration, a categorical variable was included in the final model, which estimated the effect of haemodiafiltration treatment for the first year and the effect for more than one year.

Cause-specific Cox regression models were used to examine the association between haemodiafiltration and cardiovascular mortality, and between haemodiafiltration and non-cardiovascular mortality. Competing risk analysis was considered inappropriate given the presence of time-varying covariates, since the Fine and Gray model "prohibits the introduction of any time-dependent covariate in the model when death is a competing cause of failure".[27] Variables included in the multivariable models were the same as the primary analysis. Pre-specified sub-group analyses were conducted for all-cause and cardiovascular mortality. Subgroups of interest included age, sex, diabetes, obesity, cardiovascular disease, and vascular access subtype.

A sensitivity analysis excluding centres which did not practice haemodiafiltration was also performed, as well as a sensitivity analysis adjusting for the clustering of observations within treatment centres using random effects. Proportional hazards assumptions were tested graphically and using Schoenfeld residuals. Overall fit of each model was assessed using Cox-Snell residuals.[28] Individuals with missing data for any variable in the adjusted models were excluded; no imputation was performed for missing data.

RESULTS

Study population

Between 1 January 2000 and 31 December 2014, 27,701 patients commenced haemodialysis in Australia and New Zealand (Figure 1). Of these, 269 patients were excluded due to missing haemodialysis modality data and 472 patients were excluded due to missing data pertaining to one or more covariates in the adjusted models. A total of 26,961 patients were included in the final analysis (22,774 from Australia and 4,187 from New Zealand), of whom 4,110 underwent at least one treatment with haemodiafiltration (3,302 from Australia, 808 from New Zealand). Baseline characteristics of the study population are described in Table 1. Country was a significant effect modifier of provision of haemodiafiltration; therefore, stratified analyses were conducted for Australia and New Zealand.

There were 4,110 patients who ever received haemodiafiltration, of whom 1,014 (25%) started haemodialysis with haemodiafiltration, and 3,096 (75%) switched from standard haemodialysis to haemodiafiltration after a median of 2.69 (IQR 1.50 – 4.56) years. There were 2,447 (60%) patients who permanently remained on haemodiafiltration after starting or switching, and of the 1,663 (40%) patients who did switch off haemodiafiltration, 465 (28%) eventually returned. Median follow up was 5.31 (IQR 2.87-8.36) years overall, and 3.57 (IQR 1.52-6.16) years on haemodialysis.

The final multivariable models were adjusted for age, sex, race, body mass index, year of haemodialysis start, chronic lung disease, coronary artery disease, cerebrovascular disease, peripheral vascular disease, diabetes, smoking status, vascular access type, previous

transplant, initial treatment with haemodialysis, blood flow rate, weekly treatment time, and dialysis setting. There were no significant interactions between variables.

Compared to patients who received standard haemodialysis, those receiving haemodiafiltration were more likely to be obese or diabetic, and were less likely to be Caucasian, aged ≥ 70 years, or to dialyse at home. Haemodiafiltration patients were less likely to have received a previous kidney transplant, but were more likely to have undergone prior renal replacement therapy. There was no difference in the proportion of patients with pre-existing cardiovascular disease or use of permanent vascular access between groups.

Dialysis characteristics were assessed after 12 months of stabilisation on either haemodiafiltration or standard haemodialysis (Table 2). Compared to patients receiving standard haemodialysis, a greater proportion of haemodiafiltration patients had a blood flow rate ≥350ml/min and used a high flux dialyser. A smaller proportion of haemodiafiltration patients performed quotidian (3.5+ sessions per week) or extended hour (>5 hours per session) dialysis, and fewer required erythropoietin. Vascular access and phosphate control were comparable between cohorts at 12 months.

All-cause mortality

There were 11,503 deaths during the study period (753 in the haemodiafiltration group, 10,750 in the standard haemodialysis group). The crude mortality rate was lower in patients who received haemodiafiltration compared to those managed with standard haemodialysis (8.87 vs 14.95 deaths per 100 patient-years). Crude median survival for patients on haemodiafiltration was 6.30 (IQR 3.26-11.42) years, compared to 6.26 (IQR 2.92-not

reached) years for patients who received standard haemodialysis. In the multivariable model, haemodiafiltration was independently associated with a significantly lower risk of death across both countries (HR for Australia 0.79, 95% CI 0.72-0.87, p < 0.001; HR for New Zealand 0.88, 95% CI 0.78-1.00, p =0.05) (Table 3, Figures 2-3). There was evidence of a decreasing beneficial effect of haemodiafiltration over time for patients in New Zealand (p <0.001) (Table 4). A similar pattern was observed for Australia, but there was insufficient evidence to conclude that the benefits of haemodiafiltration changed over time (p =0.09).

Cardiovascular mortality

A total of 3,957 patients died from cardiovascular causes (269 in the haemodiafiltration group, 3,688 in the standard haemodialysis group). The risk of cardiovascular death was lower in patients receiving haemodiafiltration in Australia (HR 0.78, 95% CI 0.64-0.95, p = 0.01), but not in New Zealand (HR 1.09, 95% CI 0.85-1.41, p=0.48), compared to patients managed with standard haemodialysis (Figure 3).

The cause-specific survival curves for cardiovascular and non-cardiovascular causes of death are presented in Figure 4. In both countries, haemodiafiltration was associated with a lower risk of non-cardiovascular death compared to standard haemodialysis. Haemodiafiltration was also associated with a reduced risk of cardiovascular death in Australian patients, but there was no evidence of any haemodiafiltration effect for cardiovascular death in New Zealand patients.

Subgroup analyses

There was no significant interaction between all-cause mortality and any patient subgroup in Australian patients (Figure 5). In New Zealand patients, haemodiafiltration was associated with a greater reduction in all-cause mortality in patients aged <65 years (HR 0.76, 95% CI 0.63-0.91), compared to those aged ≥65 years (HR 1.04, 95% CI 0.89-1.22; p-value for interaction 0.004)., and in diabetic patients (HR 0.84, 95% CI 0.70-1.01) more so than non-diabetic patients (HR 0.94, 95% CI 0.85-1.03; p-value for interaction <0.001).

There was no significant interaction between cardiovascular mortality and any patient subgroup in Australian patients (Figure 6). In New Zealand patients, haemodiafiltration was associated with an increased risk of cardiovascular mortality in patients aged ≥65 years (HR 1.56, 95% CI 1.23-1.99) compared to those aged <65 years (HR 0.88, 95% CI 0.63-1.22; p-value for interaction <0.001), and in non-diabetic patients (HR 1.45, 95% CI 1.19-1.78) compared to diabetic patients (HR 0.96, 95% CI 0.72-1.27; p-value for interaction <0.001).

Sensitivity analyses

When patients managed by centres which did not practice haemodiafiltration were excluded from the analysis, the association between haemodiafiltration and reduced all-cause mortality remained significant for both Australian (HR 0.79, 95% CI 0.72-0.87) and New Zealand (HR 0.88, 95% CI 0.78-1.00) patients. Similarly, there was an association between haemodiafiltration and reduced cardiovascular mortality in Australian patients (HR 0.78, 95% CI 0.64-0.95), but not in New Zealand patients (HR 1.09, 95% CI 0.85-1.41). There were no differences in outcome when clustering of observations within treatment centres was adjusted for as a random effect.

DISCUSSION

In this large, population-based cohort of patients from Australia and New Zealand who were followed for greater than 5 years, haemodiafiltration was associated with a significantly decreased risk of all-cause mortality compared to standard haemodialysis, even after adjustment for multiple potential confounders. In Australian patients, there was also an association between haemodiafiltration and reduced cardiovascular mortality, which was not demonstrated in patients from New Zealand. The beneficial effect of haemodiafiltration on survival was demonstrated across patient subgroups of age, sex, and comorbidity, and remained significant after exclusion of non-haemodiafiltration centres.

The findings of this study are in keeping with the existing observational data[6–12] and meta-analyses by Mostovaya et al[15] and Peters et al,[22] which reported an association between haemodiafiltration and decreased risks of all-cause and cardiovascular mortality compared to standard haemodialysis. However, superiority of haemodiafiltration was not confirmed by three other meta-analyses.[16–18] Nistor et al compared convective therapies (haemodiafiltration, haemofiltration, acetate-free biofiltration) to standard haemodialysis, and found no difference in all-cause mortality between groups.[16] They did report a reduction in the risk of cardiovascular mortality, which was also demonstrated by Susantitaphong et al when they compared convective therapies (high flux haemodialysis, haemofiltration or haemodiafiltration) to low flux haemodialysis.[18] No survival benefit or reduction in cardiovascular events was found in a meta-analysis by Wang et al, who compared haemodiafiltration or haemofiltration to standard haemodialysis.[17]

Inconsistency between meta-analyses may be the result of differences in study inclusion criteria or the definition of convective dialysis. Importantly, their findings must be interpreted within the limitations of their constituent studies, some of which have been criticised for being of low quality and inadequate statistical power, and high risk of bias. In contrast to the present study, the completeness and duration of patient follow-up in many of the randomised trials may have been insufficient to detect a difference in outcome between the groups, and other aspects of their methodology may have introduced bias, especially attrition bias and selective outcome reporting bias. On the other hand, the potential for residual confounding or selection bias could not be excluded from the present study, despite the use of adjusted models.

There are biologically plausible reasons why haemodiafiltration may confer a survival benefit compared to standard haemodialysis. Firstly, retention of uraemic toxins has been linked with accelerated atherosclerosis, which increases the risk of death.[3–5] Augmented removal of middle and large-sized molecules by haemodiafiltration may reduce the burden of cardiovascular disease.[29,30] Secondly, haemodiafiltration has been associated with enhanced intradialytic haemodynamic stability, potentially mediated by cooling of the extracorporeal circuit. This could protect against the development of dialysis-induced cardiac damage,[21,31] although one small randomised trial examining the intradialytic cardiac changes of haemodiafiltration did not demonstrate a reduction in regional wall motion abnormalities compared to standard haemodialysis.[32] Finally, the use of ultrapure dialysis fluid and high flux synthetic membranes allows optimal biocompatibility of the system, which is thought to reduce systemic inflammation and oxidative stress.[33–35]

The difference in the risk of cardiovascular death between Australia and New Zealand is noteworthy. Whether this finding relates to a lower number of individuals exposed to haemodiafiltration and/or to a lower number of cardiovascular death events remains uncertain. Differences in the patient population (e.g. age and proportion of patients with ischaemic heart disease) and dialysis practices (e.g. treatment time and dialysis setting) between the two countries may also have played a role. Alternatively, it may reflect residual confounding or cause of death coding bias.

This binational inception cohort study complements the existing haemodiafiltration literature as the largest observational study to be performed outside Europe. Its strengths lie in the use of a population-based approach, comprehensive multivariable models, and extended duration and completeness of follow up. However, through use of population-based data, specific details of the dialysis prescription (including convection volume, dialysate prescription, substitution modality, substitution and dialysate flow rates, and ultrafiltration rate), residual renal function, blood pressure, volume control, middle molecule clearance, and inflammation and nutrition markers cannot be known, since they are not collected by the registry. Furthermore, data on haemodialysis modality were collected annually by the registry so the exact exposure time of haemodiafiltration cannot be determined. Although residual confounding and treatment modality selection bias could not be excluded, sensitivity analyses and a thorough analytic approach were employed to minimise the potential for bias.

Although the results of this study are hypothesis generating, strong recommendations for or against the routine use of haemodiafiltration in clinical practice cannot be made. Similarly, while emerging data from post-hoc, secondary, and pooled individual participant data analyses of the randomised trials have supported a more consistent benefit in patients

receiving the highest convection volumes of haemodiafiltration,[22,36,37] superiority of this approach has not been demonstrated in an adequately powered randomised trial.

The theoretical benefit of haemodiafiltration must also be weighed against any potential risks of this modality, including the infusion of large volumes of ultrapure dialysate, or an unjustified cost to health services. The latter is a controversial issue, with the comparative cost of haemodiafiltration and high flux haemodialysis being dependent on the expense associated with disposable tubing sets, sterilising ultrafilters, and the requirement for augmented microbiological monitoring of water and dialysis fluid. Two prospective studies have reported that haemodiafiltration is either marginally more expensive or cheaper than high flux haemodialysis, depending on the choice of consumables, substitution modality, and need for additional water quality testing.[38,39] However, in cost-effectiveness analyses, which considered the worth of improved survival and health related quality of life, haemodiafiltration was considered to be a cost-effective treatment compared to both low flux haemodialysis[40] and high flux haemodialysis.[41]

In summary, the findings of this study suggest that haemodiafiltration may confer a survival advantage compared to standard haemodialysis in Australian and New Zealand patients. This benefit was independent of other factors previously associated with mortality, including treatment time, vascular access, and comorbidity burden. However, in the absence of robust, high quality evidence demonstrating a consistent benefit with haemodiafiltration compared with standard haemodialysis, widespread uptake in clinical practice is not currently supported. While this study provides further evidence that haemodiafiltration may improve outcomes, exploration of the merit and cost-effectiveness of high convection volume haemodiafiltration warrants consideration in randomised trials.

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CONFLICT OF INTEREST

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Table 1: Baseline characteristics of study cohort of 26 961 patients commencing haemodialysis between 1 January 2000 and 31 December 2014.

	Australia			**New Zealand**			**Overall**		
	Never HDF	*Ever HDF*	*Total*	*Never HDF*	*Ever HDF*	*Total*	*Never HDF*	*Ever HDF*	*Total*
Number	19 472	3302	22 774	3379	808	4187	22 851	4110	26 961
Age, years									
18-39	1,864 (10)	373 (11)	2,237 (10)	436 (13)	92 (11)	528 (13)	2,300 (10)	465 (11)	2,765 (10)
40-54	4,184 (21)	769 (23)	4,953 (22)	984 (29)	219 (27)	1,203 (29)	5,168 (23)	988 (24)	6,156 (23)
55-69	6,580 (34)	1,225 (37)	7,805 (34)	1,414 (42)	327 (40)	1,741 (42)	7,994 (35)	1,552 (38)	9,546 (35)
70+	6,844 (35)	935 (28)	7,779 (34)	545 (16)	170 (21)	715 (17)	7,389 (32)	1,105 (27)	8,494 (32)
Sex									
Female	7,584 (39)	1,234 (37)	8,818 (39)	1,260 (37)	339 (42)	1,599 (38)	8,844 (39)	1,573 (38)	10,417 (39)
Male	11,888 (61)	2,068 (63)	13,956 (61)	2,119 (63)	469 (58)	2,588 (62)	14,007 (61)	2,537 (62)	16,544 (61)
Race									
White	15,009 (77)	2,498 (76)	17,507 (77)	1,286 (38)	231 (29)	1,517 (36)	16,295 (71)	2,729 (66)	19,024 (71)
ATSI	2,200 (11)	393 (12)	2,593 (11)	1 (<1)	(0)	1 (<1)	2,201 (10)	393 (10)	2,594 (10)
MPI	479 (2)	140 (4)	619 (3)	1,883 (56)	495 (61)	2,378 (57)	2,362 (10)	635 (15)	2,997 (11)
Asian or Indian	1,254 (6)	191 (6)	1,445 (6)	171 (5)	67 (8)	238 (6)	1,425 (6)	258 (6)	1,683 (6)
Other	530 (3)	80 (2)	610 (3)	38 (1)	15 (2)	53 (1)	568 (2)	95 (2)	663 (2)
BMI, kg/m^2									
<18.5	651 (3)	66 (2)	717 (3)	51 (2)	9 (1)	60 (1)	702 (3)	75 (2)	777 (3)
18.5-30	12,814 (66)	1,871 (57)	14,685 (64)	1,663 (49)	392 (49)	2,055 (49)	14,477 (63)	2,263 (55)	16,740 (62)

>30	6,007 (31)	1,365 (41)	7,372 (32)	1,665 (49)	407 (50)	2,072 (49)	7,672 (34)	1,772 (43)	9,444 (35)
Year									
2000-2004	6,035 (31)	558 (17)	6,593 (29)	1,196 (35)	102 (13)	1,298 (31)	7,231 (32)	660 (16)	7,891 (29)
2005-2009	7,146 (37)	1,279 (39)	8,425 (37)	1,169 (35)	318 (39)	1,487 (36)	8,315 (36)	1,597 (39)	9,912 (37)
2010-2014	6,291 (32)	1,465 (44)	7,756 (34)	1,014 (30)	388 (48)	1,402 (33)	7,305 (32)	1,853 (45)	9,158 (34)
Chronic lung disease									
No	16,242 (83)	2,772 (84)	19,014 (83)	2,842 (84)	648 (80)	3,490 (83)	19,084 (84)	3,420 (83)	22,504 (83)
Yes	3,230 (17)	530 (16)	3,760 (17)	537 (16)	160 (20)	697 (17)	3,767 (16)	690 (17)	4,457 (17)
Coronary artery disease									
No	11,108 (57)	1,940 (59)	13,048 (57)	2,229 (66)	498 (62)	2,727 (65)	13,337 (58)	2,438 (59)	15,775 (59)
Yes	8,364 (43)	1,362 (41)	9,726 (43)	1,150 (34)	310 (38)	1,460 (35)	9,514 (42)	1,672 (41)	11,186 (41)
Cerebrovascular disease									
No	16,346 (84)	2,830 (86)	19,176 (84)	2,955 (87)	703 (87)	3,658 (87)	19,301 (84)	3,533 (86)	22,834 (85)
Yes	3,126 (16)	472 (14)	3,598 (16)	424 (13)	105 (13)	529 (13)	3,550 (16)	577 (14)	4,127 (15)
Peripheral vascular disease									
No	14,059 (72)	2,478 (75)	16,537 (73)	2,729 (81)	599 (74)	3,328 (79)	16,788 (73)	3,077 (75)	19,865 (74)
Yes	5,413 (28)	824 (25)	6,237 (27)	650 (19)	209 (26)	859 (21)	6,063 (27)	1,033 (25)	7,096 (26)
Diabetes mellitus									
No	10,637 (55)	1,754 (53)	12,391 (54)	1,565 (46)	321 (40)	1,886 (45)	12,202 (53)	2,075 (50)	14,277 (53)
Yes	8,835 (45)	1,548 (47)	10,383 (46)	1,814 (54)	487 (60)	2,301 (55)	10,649 (47)	2,035 (50)	12,684 (47)
Smoking history									

Never smoked	8,768 (45)	1,448 (44)	10,216 (45)	1,388 (41)	404 (50)	1,792 (43)	10,156 (44)	1,852 (45)	12,008 (45)
Current/former	10,704 (55)	1,854 (56)	12,558 (55)	1,991 (59)	404 (50)	2,395 (57)	12,695 (56)	2,258 (55)	14,953 (55)
SEIFA ranking (Australia)									
Lowest Decile	2,165 (11)	348 (11)	2,513 (11)	-	-	-	2,165 (9)	348 (8)	2,513 (9)
Middle Deciles	15,483 (80)	2,643 (80)	18,126 (80)	-	-	-	15,483 (68)	2,643 (64)	18,126 (67)
Highest Decile	1,734 (9)	303 (9)	2,037 (9)	-	-	-	1,734 (8)	303 (7)	2,037 (8)
Unclassified	81 (<1)	4 (<1)	85 (<1)	-	-	-	81 (<1)	4 (<1)	85 (<1)
Not reported	9 (<1)	4 (<1)	13 (<1)	-	-	-	9 (<1)	4 (<1)	13 (<1)
ARIA+ Category (Australia)									
Major City	13,020 (67)	2,133 (65)	15,153 (67)	-	-	-	13,020 (57)	2,133 (52)	15,153 (56)
Regional	4,796 (25)	967 (29)	5,763 (25)	-	-	-	4,796 (21)	967 (24)	5,763 (21)
Remote	692 (4)	168 (5)	860 (4)	-	-	-	692 (3)	168 (4)	860 (3)
Unclassified	955 (5)	30 (<1)	985 (4)	-	-	-	955 (4)	30 (<1)	985 (4)
Not reported	9 (<1)	4 (<1)	13 (<1)	-	-	-	9 (<1)	4 (<1)	13 (<1)
Vascular access at first HD									
Native	11,666 (60)	2,038 (62)	13,704 (60)	1,500 (44)	262 (32)	1,762 (42)	13,166 (58)	2,300 (56)	15,466 (57)
Synthetic	1,022 (5)	176 (5)	1,198 (5)	95 (3)	22 (3)	117 (3)	1,117 (5)	198 (5)	1,315 (5)
Tunneled CVC	5,921 (30)	964 (29)	6,885 (30)	1,391 (41)	423 (52)	1,814 (43)	7,312 (32)	1,387 (34)	8,699 (32)
Temporary CVC	863 (4)	124 (4)	987 (4)	393 (12)	101 (13)	494 (12)	1,256 (5)	225 (5)	1,481 (5)
Location at first HD									
Home	1,173 (6)	74 (2)	1,247 (5)	467 (14)	20 (2)	487 (12)	1,640 (7)	94 (2)	1,734 (6)

Hospital	8,355 (43)	1,370 (41)	9,725 (43)	2,053 (61)	590 (73)	2,643 (63)	10,408 (46)	1,960 (48)	12,368 (46)
Satellite	8,645 (44)	1,551 (47)	10,196 (45)	551 (16)	71 (9)	622 (15)	9,196 (40)	1,622 (39)	10,818 (40)
Not reported	1,299 (7)	307 (9)	1,606 (7)	308 (9)	127 (16)	435 (10)	1,607 (7)	434 (11)	2,041 (8)
Previous transplant									
No	15,737 (81)	2,754 (83)	18,491 (81)	2,851 (84)	760 (94)	3,611 (86)	18,588 (81)	3,514 (85)	22,102 (82)
Yes	3,735 (19)	548 (17)	4,283 (19)	528 (16)	48 (6)	576 (14)	4,263 (19)	596 (15)	4,859 (18)
Previous EPO									
No	15,737 (81)	2,754 (83)	18,491 (81)	2,851 (84)	760 (94)	3,611 (86)	18,588 (81)	3,514 (85)	22,102 (82)
Yes	3,735 (19)	548 (17)	4,283 (19)	528 (16)	48 (6)	576 (14)	4,263 (19)	596 (15)	4,859 (18)
Blood flow rate									
< 250ml/min	1,853 (10)	218 (7)	2,071 (9)	478 (14)	69 (9)	547 (13)	2,331 (10)	287 (7)	2,618 (10)
250-299ml/min	4,827 (25)	747 (23)	5,574 (24)	1,204 (36)	413 (51)	1,617 (39)	6,031 (26)	1,160 (28)	7,191 (27)
300-349ml/min	10,216 (52)	1,816 (55)	12,032 (53)	1,346 (40)	291 (36)	1,637 (39)	11,562 (51)	2,107 (51)	13,669 (51)
350+ ml/min	2,576 (13)	521 (16)	3,097 (14)	351 (10)	35 (4)	386 (9)	2,927 (13)	556 (14)	3,483 (13)
Treatment time									
<12 hr/week	1,548 (8)	251 (8)	1,799 (8)	125 (4)	21 (3)	146 (3)	1,673 (7)	272 (7)	1,945 (7)
12-12.9 hr/week	8,876 (46)	1,344 (41)	10,220 (45)	1,359 (40)	419 (52)	1,778 (42)	10,235 (45)	1,763 (43)	11,998 (45)
13-13.9 hr/week	2,342 (12)	498 (15)	2,840 (12)	340 (10)	145 (18)	485 (12)	2,682 (12)	643 (16)	3,325 (12)
14+ hr/week	4,473 (23)	766 (23)	5,239 (23)	1,069 (32)	93 (12)	1,162 (28)	5,542 (24)	859 (21)	6,401 (24)
Not reported	2,233 (11)	443 (13)	2,676 (12)	486 (14)	130 (16)	616 (15)	2,719 (12)	573 (14)	3,292 (12)
Cause of ESKD									

Diabetes	6,598 (34)	1,184 (36)	7,782 (34)	1,587 (47)	437 (54)	2,024 (48)	8,185 (36)	1,621 (39)	9,806 (36)
Glomerulonephritis	4,497 (23)	776 (24)	5,273 (23)	771 (23)	153 (19)	924 (22)	5,268 (23)	929 (23)	6,197 (23)
Cystic disease	1,219 (6)	232 (7)	1,451 (6)	181 (5)	20 (2)	201 (5)	1,400 (6)	252 (6)	1,652 (6)
Renovascular	2,849 (15)	458 (14)	3,307 (15)	322 (10)	83 (10)	405 (10)	3,171 (14)	541 (13)	3,712 (14)
Other	8,570 (44)	1,386 (42)	9,956 (44)	1,214 (36)	254 (31)	1,468 (35)	9,784 (43)	1,640 (40)	11,424 (42)
Not reported	53 (<1)	18 (<1)	71 (<1)	22 (<1)	1 (<1)	23 (<1)	75 (<1)	19 (<1)	94 (<1)

ARIA+, Accessibility/Remoteness Index of Australia; ATSI, Aboriginal or Torres Strait Islander; BMI, body mass index; CVC, central venous catheter; EPO, erythropoietin; ESKD, end stage kidney disease; HD, haemodialysis; HDF, haemodiafiltration; MPI, Maori or Pacific Islander; RRT, renal replacement therapy; SEIFA, Socio-Economic Index For Australia.

Table 2: Dialysis characteristics following 12 months of stabilisation of 18,972 incident patients commencing haemodiafiltration or standard haemodialysis between 1 January 2000 and 31 December 2014.

	Australia			**New Zealand**			**Overall**		
	HD	*HDF*	*Total*	*HD*	*HDF*	*Total*	*HD*	*HDF*	*Total*
Total	15,242	985	16,227	2,455	290	2,745	17,697	1,275	18,972
Last vascular access									
Native	12,164 (80)	816 (83)	12,980 (80)	1,806 (74)	173 (60)	1,979 (72)	13,970 (79)	989 (78)	14,959 (79)
Synthetic	1,289 (8)	67 (7)	1,356 (8)	127 (5)	8 (3)	135 (5)	1,416 (8)	75 (6)	1,491 (8)
Central venous catheter	1,789 (12)	102 (10)	1,891 (12)	522 (21)	109 (38)	631 (23)	2,311 (13)	211 (17)	2,522 (13)
Blood flow rate									
<250 mL/min	562 (4)	17 (2)	579 (4)	188 (8)	9 (3)	197 (7)	750 (4)	26 (2)	776 (4)
250-299 mL/min	2,433 (16)	103 (10)	2,536 (16)	598 (24)	82 (28)	680 (25)	3,031 (17)	185 (15)	3,216 (17)
300-349 mL/min	8,849 (58)	564 (57)	9,413 (58)	1,186 (48)	169 (58)	1,355 (49)	10,035 (57)	733 (57)	10,768 (57)
350+ mL/min	3,398 (22)	301 (31)	3,699 (23)	483 (20)	30 (10)	513 (19)	3,881 (22)	331 (26)	4,212 (22)
Haemodialyser type									
Low flux	4,378 (29)	8 (<1)	4,386 (27)	1,438 (59)	0 (0)	1,438 (52)	5,816 (33)	8 (<1)	5,824 (31)
High flux	10,863 (71)	977 (99)	11,840 (73)	1,017 (41)	290 (100)	1,307 (48)	11,880 (67)	1,267 (99)	13,147 (69)
Not reported	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
Treatment time (per session)									
<3 hours	71 (<1)	6 (<1)	77 (<1)	2 (<1)	0 (0)	2 (<1)	73 (<1)	6 (<1)	79 (<1)
3-3.9 hours	892 (6)	57 (6)	949 (6)	82 (3)	8 (3)	90 (3)	974 (6)	65 (5)	1,039 (5)

4-4.9 hours	9,497 (62)	608 (62)	10,105 (62)	1,303 (53)	236 (81)	1,539 (56)	10,800 (61)	844 (66)	11,644 (61)
5+ hours	4,781 (31)	314 (32)	5,095 (31)	1,068 (44)	46 (16)	1,114 (41)	5,849 (33)	360 (28)	6,209 (33)
Not reported	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
Frequency									
<3 per week	370 (2)	22 (2)	392 (2)	35 (1)	3 (1)	38 (1)	405 (2)	25 (2)	430 (2)
3-3.4 per week	13,898 (91)	938 (95)	14,836 (91)	2,170 (88)	284 (98)	2,454 (89)	16,068 (91)	1,222 (96)	17,290 (91)
3.5-3.9 per week	403 (3)	1 (<1)	404 (2)	102 (4)	0 (0)	102 (4)	505 (3)	1 (<1)	506 (3)
4+ per week	570 (4)	24 (2)	594 (4)	148 (6)	3 (1)	151 (6)	718 (4)	27 (2)	745 (4)
Not reported	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
Estimated minimum convection volume [1]									
<17 L	-	588 (60)	-	-	238 (82)	-	-	826 (65)	-
17-19 L	-	261 (26)	-	-	31 (11)	-	-	292 (23)	-
20-22 L	-	92 (9)	-	-	9 (3)	-	-	101 (8)	-
22+ L	-	44 (4)	-	-	12 (4)	-	-	56 (4)	-
Phosphate									
<1.6 mmol/L	7,222 (47)	477 (48)	7,699 (47)	817 (33)	113 (39)	930 (34)	8,039 (45)	590 (46)	8,629 (45)
1.6+ mmol/L	7,115 (47)	500 (51)	7,615 (47)	1,494 (61)	177 (61)	1,671 (61)	8,609 (49)	677 (53)	9,286 (49)
Not reported	905 (6)	8 (<1)	913 (6)	144 (6)	0 (0)	144 (5)	1,049 (6)	8 (<1)	1,057 (6)
Haemoglobin									
<100 g/L	2,106 (14)	121 (12)	2,227 (14)	506 (21)	62 (21)	568 (21)	2,612 (15)	183 (14)	2,795 (15)
100-119 g/L	7,401 (49)	528 (54)	7,929 (49)	1,122 (46)	157 (54)	1,279 (47)	8,523 (48)	685 (54)	9,208 (49)

120+ g/L	5,682 (37)	336 (34)	6,018 (37)	822 (33)	71 (24)	893 (33)	6,504 (37)	407 (32)	6,911 (36)
Not reported	53 (<1)	0 (0)	53 (<1)	5 (<1)	0 (0)	5 (<1)	58 (<1)	0 (0)	58 (<1)
Erythropoietin use									
Yes	3,025 (20)	160 (16)	3,185 (20)	706 (29)	42 (14)	748 (27)	3,731 (21)	202 (16)	3,933 (21)
No	12,217 (80)	825 (84)	13,042 (80)	1,749 (71)	248 (86)	1,997 (73)	13,966 (79)	1,073 (84)	15,039 (79)

HD, haemodialysis; HDF, haemodiafiltration; [1] For HDF patients only, calculated using the formula: blood flow rate (L/min) × treatment time per session (min) × 0.20 (minimum filtration fraction).

Table 3: Multivariable Cox regression analysis of survival in 26 961 patients who commenced haemodialysis in Australia and New Zealand between 2000 and 2014.

Covariates	Australia			New Zealand		
	HR	*95% CI*	*P-value*	*HR*	*95% CI*	*P-value*
Haemodiafiltration			<0.001			0.05
No	1.00	-		1.00	-	
Yes	0.79	0.72 - 0.87		0.88	0.78 - 1.00	
Age			<0.001			<0.001
18-39	1.00	-		1.00	-	
40-54	1.49	1.29 - 1.72		1.11	0.96 - 1.28	
55-69	1.87	1.64 - 2.14		1.51	1.23 - 1.84	
70+	2.75	2.38 - 3.18		2.15	1.74 - 2.67	
Sex			<0.001			<0.001
Female	1.00	-		1.00	-	
Male	1.14	1.08 - 1.19		1.19	1.15 - 1.23	
Race			<0.001			<0.001
White	1.00	-		1.00	-	
Aboriginal or Torres Strait Islander	1.04	0.91 - 1.20		-	-	
Maori or Pacific Islander	0.73	0.64 - 0.84		0.97	0.85 - 1.11	
Asian or Indian	0.63	0.59 - 0.68		0.74	0.67 - 0.82	
Other	0.69	0.57 - 0.83		0.86	0.65 - 1.13	
BMI			<0.001			0.004
0-18.4 (Underweight)	1.44	1.27 - 1.63		1.39	1.02 - 1.90	
18.5-29.9 (Normal-Overweight)	1.00	-		1.00	-	
30+ (Obese-Extremely Obese)	0.88	0.83 - 0.93		1.07	1.00 - 1.14	
Vascular access			<0.001			<0.001
Native	1.00	-		1.00	-	
Synthetic	1.12	*1.04 - 1.21*		1.07	*0.90 - 1.26*	
Tunneled CVC	1.89	1.75 - 2.03		1.67	1.48 - 1.87	

Covariates	Australia			New Zealand		
	HR	*95% CI*	*P-value*	*HR*	*95% CI*	*P-value*
Temporary CVC	2.18	1.82 - 2.61		1.99	1.59 - 2.49	
ESKD start			<0.001			0.1
2000-2004	1.00	-		1.00	-	
2005-2009	0.92	0.86 - 0.97		0.94	0.88 - 1.00	
2010-2014	0.87	0.80 - 0.94		0.92	0.73 - 1.15	
Chronic lung disease			<0.001			<0.001
No	1.00	-		1.00	-	
Yes	1.27	1.21 - 1.32		1.22	1.09 - 1.37	
Coronary artery disease			<0.001			<0.001
No	1.00	-		1.00	-	
Yes	1.30	1.23 - 1.37		1.58	1.47 - 1.71	
Cerebrovascular disease			<0.001			0.01
No	1.00	-		1.00	-	
Yes	1.27	1.20 - 1.33		1.16	1.03 - 1.31	
Peripheral vascular disease			<0.001			<0.001
No	1.00	-		1.00	-	
Yes	1.25	1.18 - 1.31		1.26	1.11 - 1.42	
Diabetes (any type)			<0.001			0.004
No	1.00	-		1.00	-	
Yes	1.26	1.19 - 1.33		1.15	1.05 - 1.27	
Smoking status			0.01			0.001
Never smoked	1.00	-		1.00	-	
Current/former	1.06	1.01 - 1.11		1.17	1.07 - 1.28	
Previous transplant			<0.001			<0.001
No	1.00	-		1.00	-	
Yes	0.47	0.39 - 0.56		0.38	0.27 - 0.54	
Initial treatment with HD			0.8			0.04

Covariates	Australia			New Zealand		
	HR	*95% CI*	*P-value*	*HR*	*95% CI*	*P-value*
No	1.00	-		1.00	-	
Yes	0.99	0.93 - 1.06		0.88	0.78 - 1.00	
Blood flow rate			<0.001			<0.001
Less than 250ml/min	1.00	-		1.00	-	
250-299ml/min	0.89	0.76 - 1.04		0.65	0.51 - 0.81	
300-349ml/min	0.75	0.61 - 0.91		0.54	0.44 - 0.66	
350ml/min or more	0.65	0.53 - 0.79		0.59	0.46 - 0.75	
Treatment time			<0.001			<0.001
Each additional hour per week	0.93	0.92 - 0.94		0.95	0.93 - 0.97	
Dialysis location			<0.001			<0.001
Home	0.56	0.48 - 0.65		0.57	0.46 - 0.71	
Hospital	1.00	-		1.00	-	
Satellite	0.64	0.59 - 0.70		0.61	0.50 - 0.74	

[1] For the New Zealand analysis, Aboriginal and Torres Strait Islander was categorized as Other. ATSI, Aboriginal or Torres Strait Islander; BMI, body mass index; CVC, central venous catheter; haemodialysis, haemodialysis; haemodiafiltration, haemodiafiltration; MPI, Maori or Pacific Islander; RRT, renal replacement therapy; SEIFA, Socio-Economic Index For Australia.

Table 4: Multivariable Cox regression model comparing all-cause mortality and multivariable cause-specific regression models comparing cardiovascular and non-cardiovascular mortality for an overall effect of haemodiafiltration compared to a difference in effect between the first 12 months of haemodialysis and subsequent years

Country	Outcome	Overall effect		Haemodiafiltration effect over time		
		HR (95%CI)	*P-value*	*First 12 months HR (95%CI)*	*More than one year HR (95%CI)*	*P-value for change over time*
Australia	All-cause mortality	0.79 (0.72, 0.87)	<0.001	0.55 (0.35, 0.87)	0.81 (0.74, 0.89)	0.09
Australia	Cardiovascular mortality	0.79 (0.65, 0.96)	0.01	0.71 (0.38, 1.34)	0.80 (0.66, 0.96)	0.76
Australia	Non-cardiovascular mortality	0.80 (0.73, 0.88)	<0.001	0.74 (0.56, 0.99)	0.82 (0.74, 0.90)	0.53
New Zealand	All-cause mortality	0.88 (0.78, 1.00)	0.05	0.67 (0.54, 0.83)	0.90 (0.79, 1.03)	0.01
New Zealand	Cardiovascular mortality	1.09 (0.85, 1.41)	0.48	0.59 (0.38, 0.91)	1.21 (0.91, 1.60)	0.002
New Zealand	Non-cardiovascular mortality	0.77 (0.70, 0.86)	<0.001	0.56 (0.45, 0.70)	0.82 (0.72, 0.94)	0.007

FIGURE LEGENDS

Figure 1 Inception cohort patients included in analysis.

Figure 2 Modelled survival curves comparing patient survival between 4110 patients managed with haemodiafiltration and 22 851 patients managed with haemodialysis by country. The difference between the groups was statistically significant for Australia ($p<0.001$) and New Zealand ($p<0.001$).

Figure 3 Multivariable Cox regression model comparing all-cause mortality and multivariable cause-specific regression models comparing cardiovascular and non-cardiovascular mortality between 4110 patients managed with haemodiafiltration and 22 851 patients managed with standard haemodialysis by country.

Figure 4 Multivariable cause-specific regression models comparing cardiovascular and non-cardiovascular mortality between 4110 patients managed with haemodiafiltration and 22 851 patients managed with standard haemodialysis by country.

Figure 5 Multivariable Cox regression model comparing all-cause mortality by patient subgroup in 4110 patients managed with haemodiafiltration and 22 851 patients managed with standard haemodialysis by country.

Figure 6 Multivariable Cox regression model comparing cardiovascular mortality by patient subgroup in 4110 patients managed with haemodiafiltration and 22 851 patients managed with standard haemodialysis by country.

Figure 1. Inception cohort patients included in analysis.

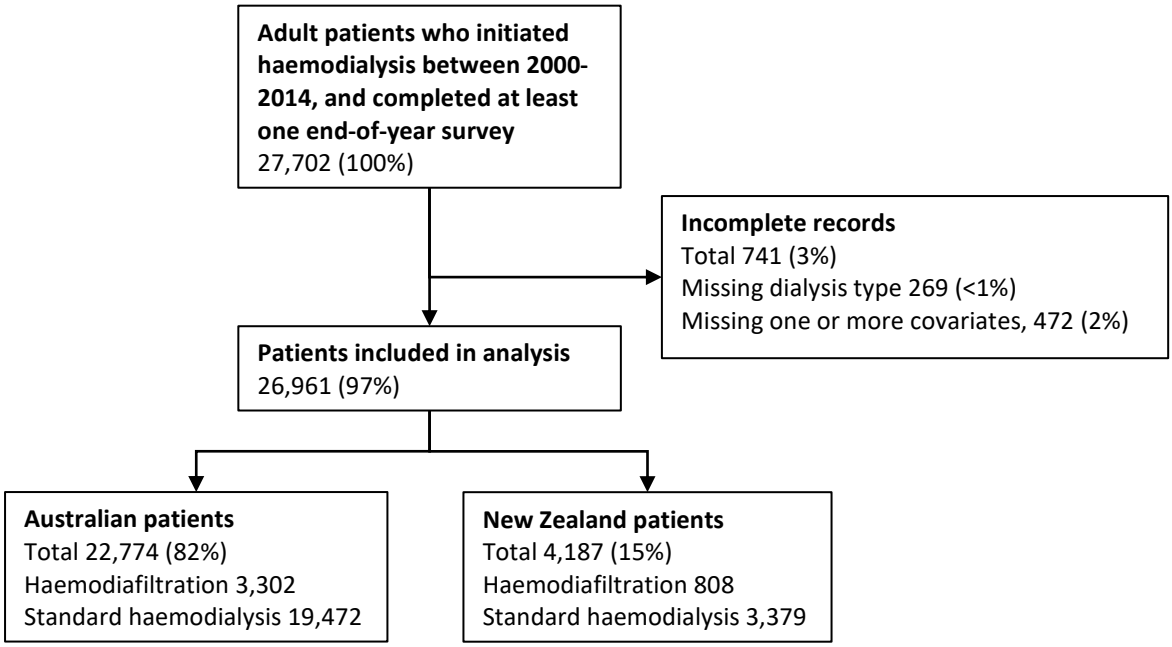
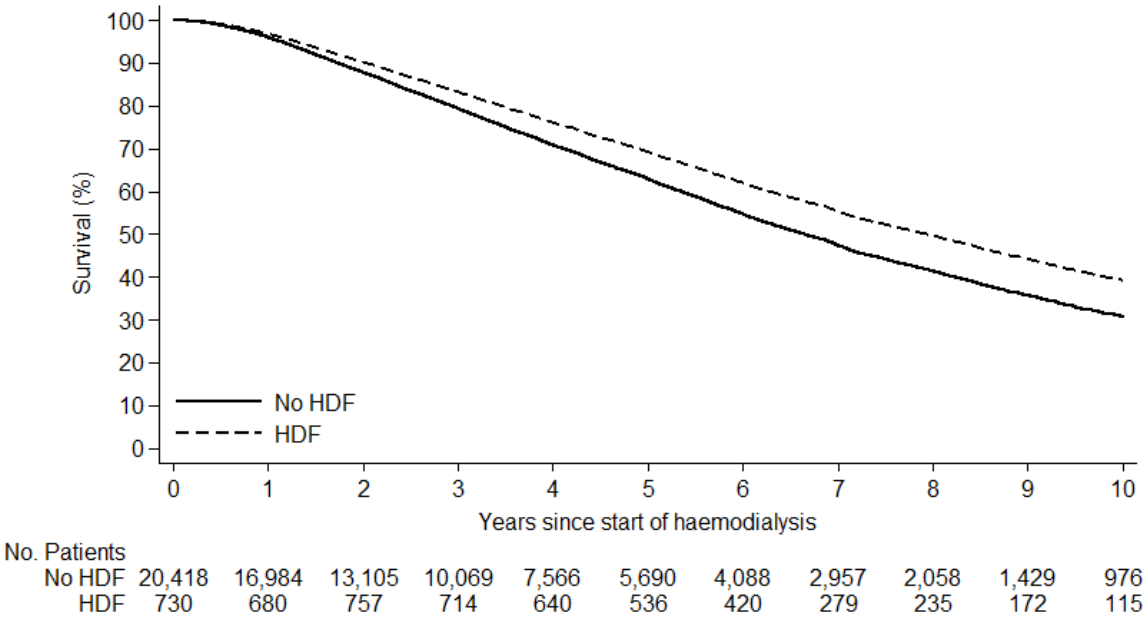
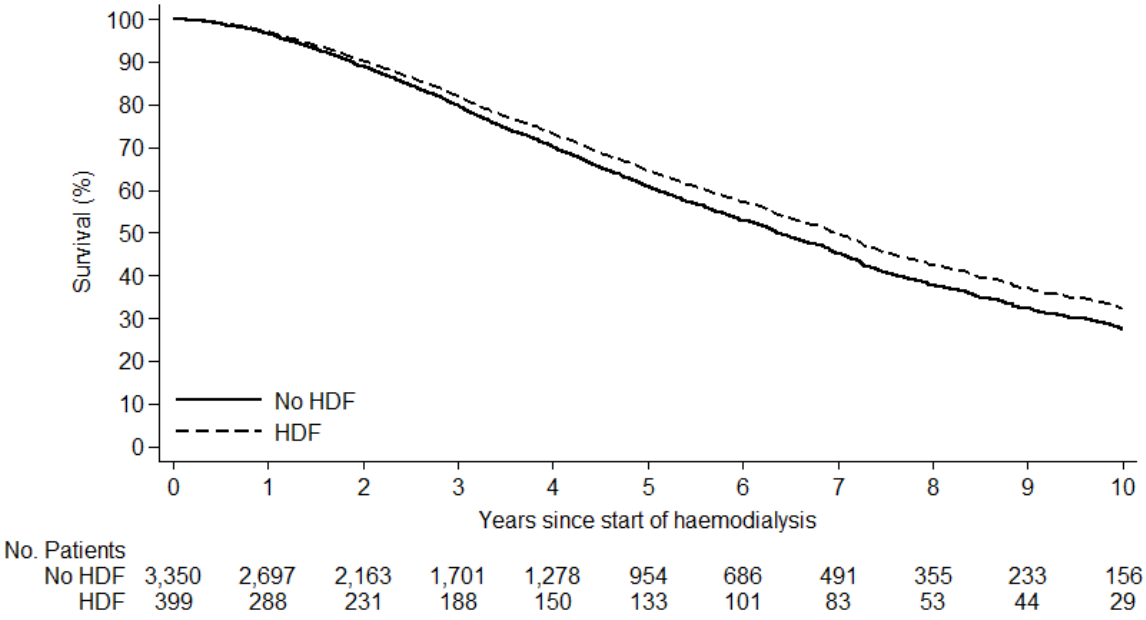


Figure 2. Modelled survival curves comparing patient survival between 4110 patients managed with haemodiafiltration and 22851 patients managed with haemodialysis by country. The difference between the groups was statistically significant for Australia (p<0.001) and New Zealand (p<0.001).



A: Australia



B: New Zealand

Figure 3. Multivariable Cox regression model comparing all-cause mortality and multivariable cause-specific regression models comparing cardiovascular and non-cardiovascular mortality between 4110 patients managed with haemodiafiltration and 22 851 patients managed with standard haemodialysis by country.

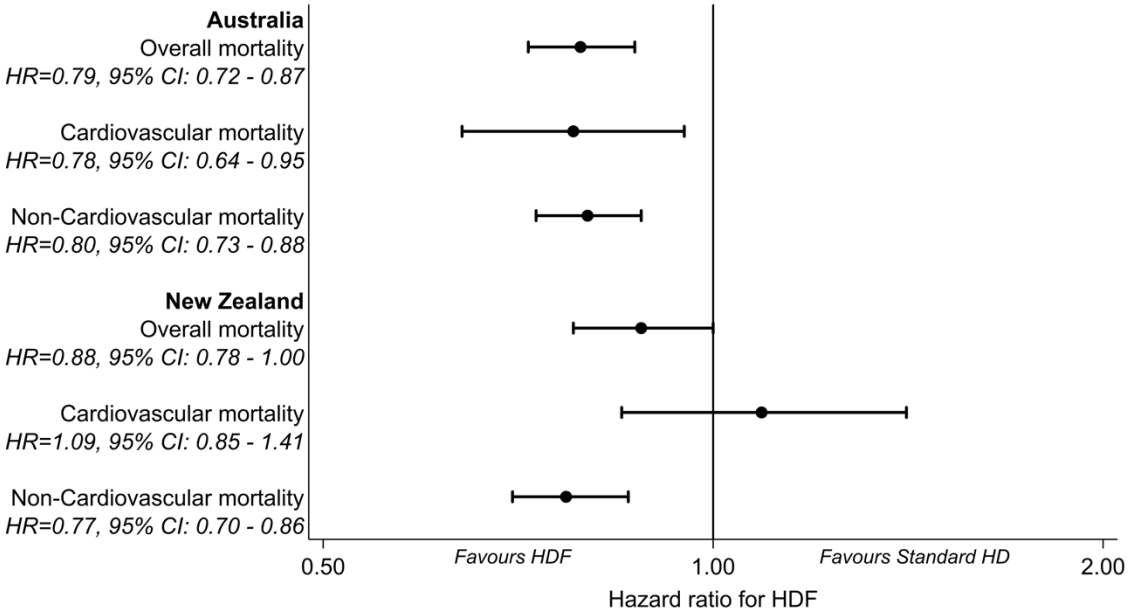
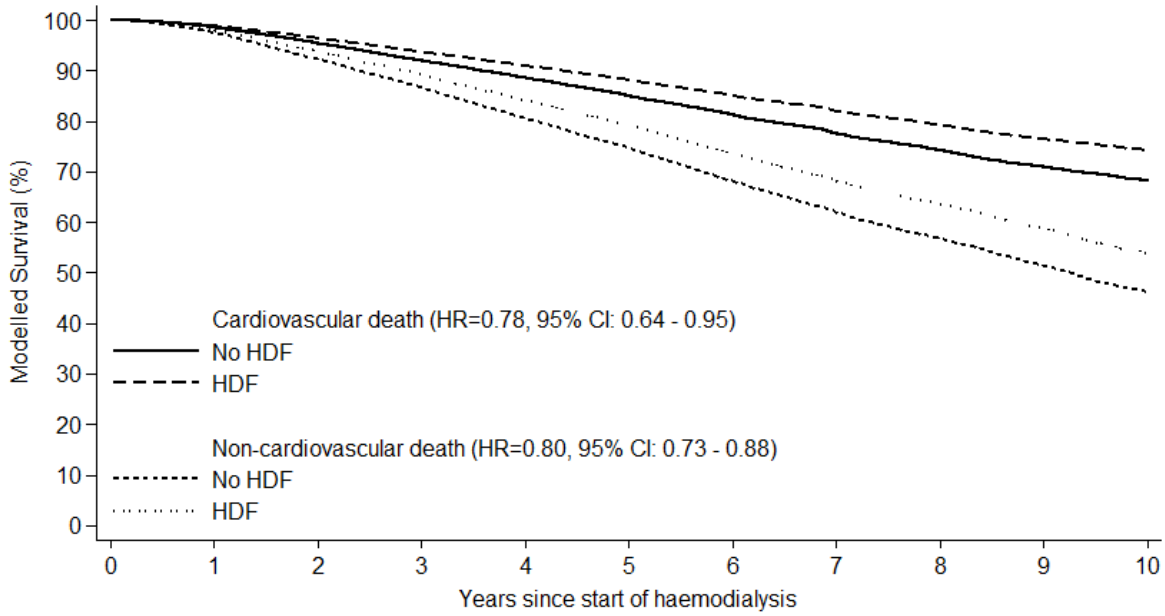
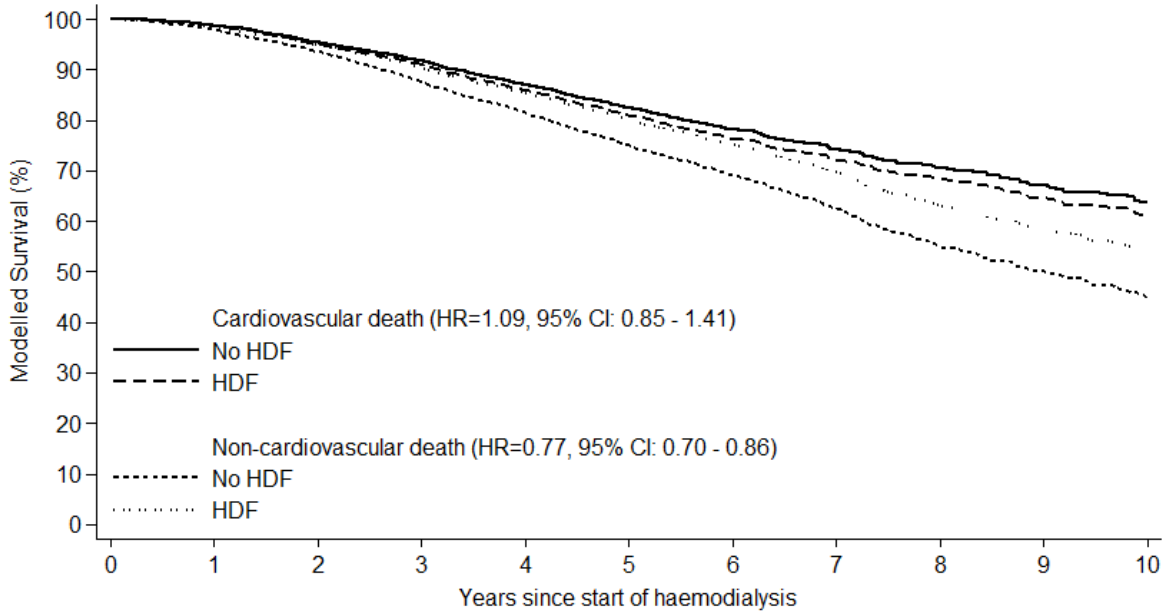


Figure 4. Cause-specific survival curves comparing cardiovascular and non-cardiovascular mortality between 4110 patients managed with haemodiafiltration and 22 851 patients managed with standard haemodialysis by country.

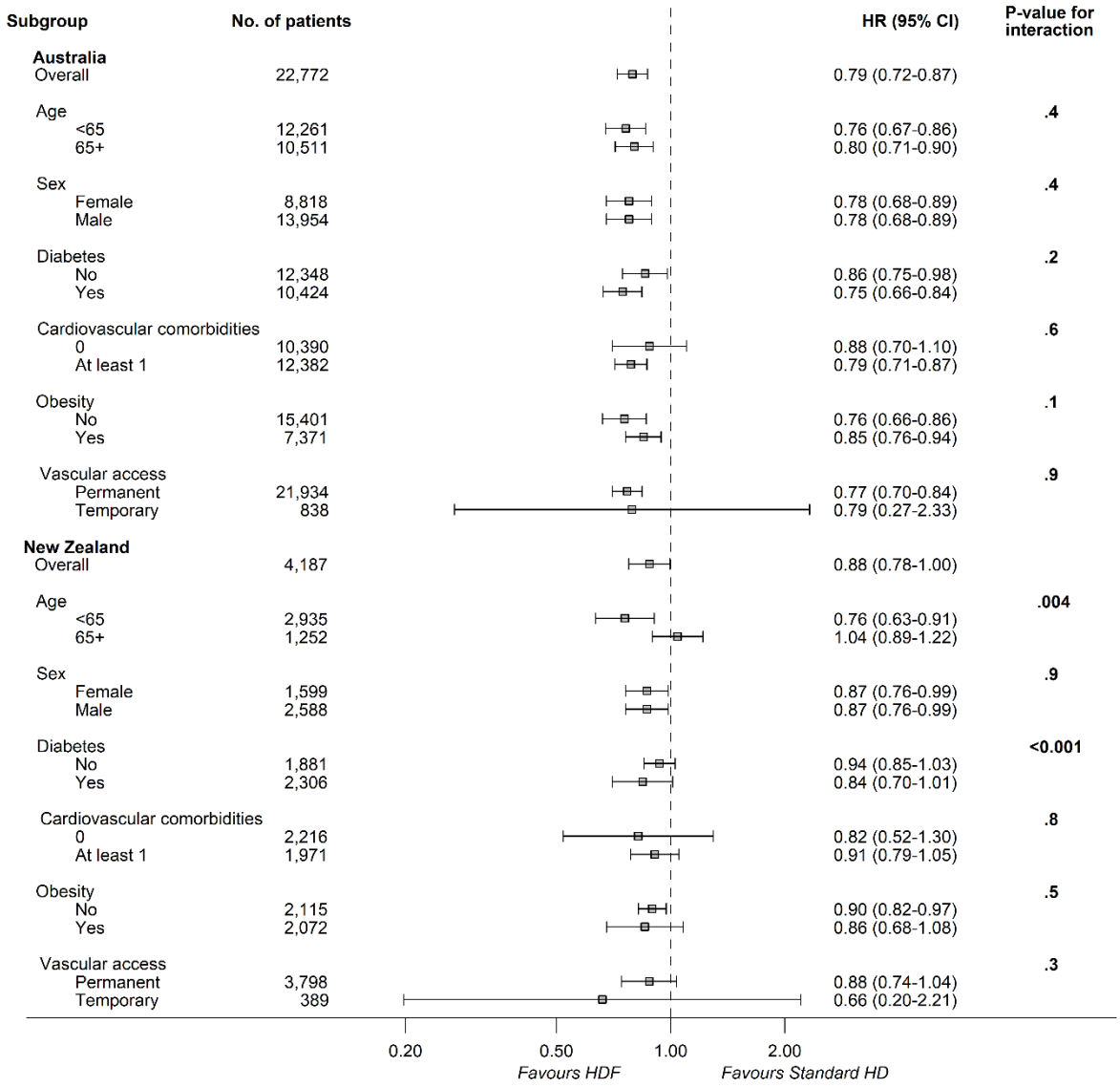


A: Australia



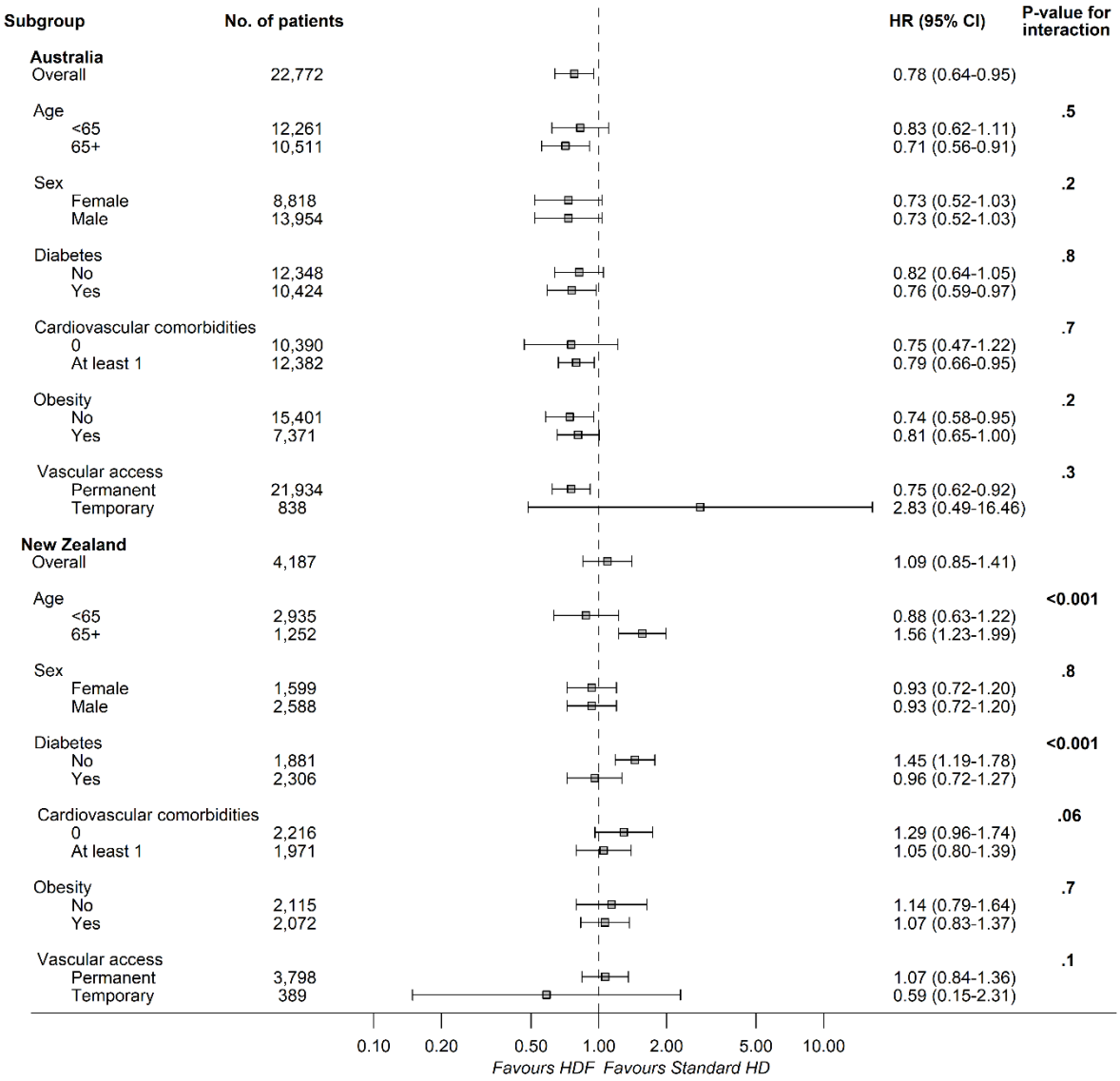
B: New Zealand

Figure 5. Multivariable Cox regression model comparing all-cause mortality by patient subgroup in 4110 patients managed with haemodiafiltration and 22 851 patients managed with standard haemodialysis by country.



Estimates shown include hazard ratio with 95% confidence intervals. P-value for interaction reports significant differences between subgroups and the outcome of interest.

Figure 6. Multivariable Cox regression model comparing cardiovascular mortality by patient subgroup in 4110 patients managed with haemodiafiltration and 22 851 patients managed with standard haemodialysis by country.



Estimates shown include hazard ratio with 95% confidence intervals. P-value for interaction reports significant differences between subgroups and the outcome of interest.