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Comparing survival in patients with chronic kidney disease across three countries – Results from the study of heart and renal protection-extended review

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Abstract

Aim: This study examined whether survival and causes of death differed between participants enrolled from Australia (AUS), Malaysia (MYL), and New Zealand (NZ) in extended follow-up of the Study of Heart and Renal Protection (SHARP), a randomized controlled trial (RCT) of participants with moderate to severe chronic kidney disease comparing placebo to combination therapy with Simvastatin and Ezetimibe.

Methods: All participants alive at final SHARP study visit in participating centres were eligible for inclusion. Consenting participants were re-enrolled following final SHARP Study visit and followed for 5 years. Data collection included: significant medical events, hospital admissions and requirement for kidney replacement therapy. Data linkage was performed to national kidney and mortality registries. The primary outcome was all-cause mortality compared across the three countries.

Results: The SHARP trial randomized 2029 participants from AUS (1043/2029, 51%), MYL (701/2029, 35%), and NZ (285/2029, 14%), with 1136 participants alive and eligible for extended follow-up at the end of SHARP. In multivariable analysis, risk of death was increased for participants in MYL (HR 1.37, 95% CI 1.17–1.61, $p < .001$) and NZ (HR 1.28, 95% CI 1.04–1.57, $p = .02$) when compared to AUS participants. Adjustment for kidney transplantation as a competing risk did not explain the variation seen between countries.

Conclusion: This study allows a better understanding of the differences in long-term mortality risk across participants from AUS, MYL, and NZ in extended follow-up of the SHARP study and demonstrates the feasibility and value of extended follow-up of participants enrolled in RCTs.

KEYWORDS
cardiovascular disease, chronic kidney disease, extended follow-up, international comparison, mortality

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Summary at a glance

This study has identified differences in long-term mortality risk between participants enrolled from Australia, Malaysia and New Zealand in extended follow-up of the Study of Heart and Renal Protection (SHARP), a randomized controlled trial comparing placebo to combination therapy with Simvastatin and Ezetimibe in participants with chronic kidney disease.

1 | INTRODUCTION

Chronic kidney disease (CKD) is present in around 10% of the population and was ranked as the 12th leading cause of death in 2017.[1] The bulk of this mortality and morbidity is seen in populations with advanced CKD, who are near to, or requiring, dialysis or transplantation. This burden is manifested by increases in cancer, infections and cardiovascular diseases which may vary across regions and countries. Systematic data, such as that from the extended follow-up of multinational randomized trials, offers a valuable tool to examine comparable populations, to understand differences in outcomes across different regions and their likely aetiology.

The majority of trans-national comparisons of practice and outcomes in CKD arise from the analysis of patient registries. Whilst valuable, such comparisons struggle to adjust for practice differences between countries, and patients with non-dialysis dependent CKD are usually excluded from most registries and analyses. Other initiatives, such as the Dialysis Outcomes and Practice Patterns Study (DOPPS), have further highlighted variation in international practice patterns and outcomes in haemodialysis, peritoneal dialysis and CKD.[2–4] Clinical trials, with their multinational reach and standardized inclusion criteria, can overcome some of the challenges of comparing kidney replacement therapy registry analyses and allow new, valuable comparisons. Long term follow up of such studies can improve the precision of estimates and may provide unique insights such as detection of benefits or harms of interventions which are only captured during the extended phase of data collection.[5]

The Study of Heart and Renal Protection (SHARP) was a randomized controlled trial of 9270 participants with moderate to severe CKD in 18 countries, comparing placebo to combination therapy with Simvastatin and Ezetimibe. The SHARP Extended Review (SHARP-ER) study is part of the broader SHARP post-Trial Follow-UP (PTFU) and extended the follow up of eligible participants in the Asia-Pacific region, including participants from Australia, Malaysia, and New Zealand, for a further 5 years. The aim of this analysis was to examine whether survival and causes of death differed between participants enrolled from these three countries.

2 | METHODS

2.1 | Study design

Descriptions of the SHARP and SHARP-ER study designs have been previously published.[6,7] In brief, the SHARP trial recruited participants aged 40 years or older with CKD (defined as at least one measurement of serum creatinine >150 μmol/L in men or 130 μmol/L in women) with no known history of myocardial infarction or coronary revascularisation between 2003 and 2006. Participants were randomized in the ratio of 4:4:1 to; a combination of simvastatin and ezetimibe, matching placebo or simvastatin alone. Those allocated to simvastatin alone were re-randomized after 1 year to one of the other two comparison arms. After initial randomization, participants were followed up for at least 4 years.

The SHARP-ER study extended follow up of participants alive at the final SHARP study visit in participating centres in Australia, Malaysia, and New Zealand for a further 5 years. All participants in enrolled centres who were not previously documented as having withdrawn consent were eligible for inclusion in SHARP-ER. Exclusion criteria for SHARP-ER included: the presence of a concomitant major illness that would limit the participant's follow up (in the opinion of the treating physician), a high likelihood that the participant would not adhere to follow up, or an inability to provide informed consent for reasons of mental or physical incapacity. The study was conducted in accordance with the approved study protocol, the principles of the "Declaration of Helsinki" and the laws and regulations of the relevant countries. All participating centres obtained independent ethics approval prior to study commencement.

The primary outcome of this analysis was all-cause mortality compared across the three countries participating in SHARP-ER, including adjustment for the competing risk of kidney transplantation, with the secondary outcome being cause of death.

2.2 | SHARP-ER Study procedures

Consenting participants were re-enrolled at between 1.5 and 2 years following their final SHARP Study visit, then followed up on a 6-monthly basis until 5 years after their final SHARP Study visit. Data collection was extensive, including: the occurrence of significant medical events or admissions to hospital, and the requirement for chronic dialysis or kidney transplantation. Data linkage was performed for eligible participants to national kidney and mortality registries in the three countries.

2.3 | Variables of interest

The main study exposure for this analysis was country of enrolment. Baseline demographic and laboratory variables were recorded at

participants' original SHARP enrolment, including; country of enrolment, comorbid conditions and baseline Kidney Disease Improving Global Outcomes (KDIGO)[8] stage of CKD or dialysis requirement. Treatment allocation during the SHARP trial was recorded and classified as per final treatment allocation, that is, treatment arm versus placebo arm rather than initial randomization which included three arms (a combination of simvastatin and ezetimibe, matching placebo or simvastatin alone).

The outcomes were derived through routine adverse event reporting during the SHARP study and through questionnaire responses and data linkage during the SHARP-ER phase of follow up. All participants were followed from randomization date at SHARP commencement until date of death, date of the final SHARP visit for participants not enrolled in SHARP-ER, or the 1st January 2016 for those enrolled in SHARP-ER. Due to differing sources of death data, all recorded causes of death were re-coded into comparable categories that were consistent with kidney registry mortality reporting. All adjudications were made by two independent reviewers, with any disagreement determined by a third adjudicator.

2.4 | Statistical analysis

Results are reported as counts and percentages for categorical variables, mean ± standard deviation for normally distributed continuous variables and median with interquartile range for non-parametrically distributed continuous variables. Multivariable Cox regression models were constructed to identify the hazard ratios (HRs) for mortality as a function of country of enrolment and with adjustment for additional baseline covariates. Variables were included in the model based on clinical judgement and univariate assessment of each variable. The final model included; country (Australia set as the reference group due to the largest sample size), age, sex, comorbidities (diabetes and cerebrovascular disease), stage of CKD at SHARP enrolment (stage III [eGFR 30–59 ml/min/1.73 m^2], IV [eGFR 15–29 ml/min/1.73 m^2], V [eGFR < 15 ml/min/1.73 m^2], or maintenance dialysis, with stage III set as the baseline group) and final SHARP treatment allocation. The assumption of proportional hazards was tested by including time-dependent covariates in the model and plotting Schoenfeld residuals which supported the assumption of proportional hazards. Interactions were examined for variables within the models. Competing risk analyses were undertaken using multivariable Fine and Gray sub-distribution hazards models[9] to assess the sub-distribution hazard ratios (SHRs) of all-cause mortality as a function of country of enrolment while treating transplantation as a competing risk. Statistical analyses were performed using Stata software (release 15.1, StataCorp, College Station, TX). Adjusted HRs or SHRs and 95% confidence intervals are presented, a two-sided *p*-value <.05 was considered statistically significant. Comparison of differing causes of death between participants from included countries are presented descriptively. Whilst treatment allocation at baseline was included in the multivariable models for adjustment, the effect of treatment allocation on mortality has not been reported in this study pending the broader SHARP PTFU analyses.

3 | RESULTS

3.1 | Participants

The SHARP trial randomized 2029 participants from Australia, New Zealand, and Malaysia, with 397 of these censored from this survival analysis at the end of the SHARP study (Figure 1). The majority of censored participants were from Australia (315/397, 79%). The median follow-up of all participants was 7 years (interquartile range [IQR]; 4–11 years) and was longer in Malaysian participants than other countries (Figure 2). The proportion of surviving SHARP participants enrolled in SHARP-ER varied by country; 60% ($n = 468/783$) of Australian participants, 100% ($n = 535/537$) of Malaysian participants and 62% ($n = 133/213$) of New Zealand participants.

3.2 | Cohort characteristics

The baseline characteristics of all SHARP participants from Australia, Malaysia, and New Zealand are presented in Table 1. Whilst the participants from Malaysia (55 years [IQR 47–63]) were younger than those from Australia (65 years [IQR 54–75]) and New Zealand (63 years [IQR 54–70]), they had higher blood pressure, more diabetes, more advanced CKD and heavier albuminuria. Fewer of the Malaysian patients had a history of cerebrovascular disease. Treatment allocation during the SHARP trial was not different between groups (Table 1), however reported rates of cholesterol lowering therapy in the SHARP-ER data collection did vary by country (Table S1).

The baseline characteristics of censored participants were similar to those of non-censored participants (Table S2), with similar rates of comorbidity, severity of kidney dysfunction and degree of albuminuria.

3.3 | Primary outcome—all-cause mortality

3.3.1 | Unadjusted analyses

There was no evidence of difference between countries in rates of all-cause mortality in unadjusted analyses for either Malaysia (HR 0.93, 0.81–1.07, $p = .32$) or New Zealand (HR 1.00, 0.81–1.23, $p = .98$) when compared to Australia (Figure 2). Results of univariate Cox proportional hazards modelling of all-cause mortality are presented in Table S3 and showed that; age, stage of CKD, diabetes and cerebrovascular disease at enrolment were all associated with higher mortality risk.

3.3.2 | Multivariable analyses

The results of multivariable Cox proportional hazards models evaluating the effect of country of enrolment and baseline covariates on all-cause mortality are summarized in Table 2. These show an increased risk of death for participants in Malaysia (HR 1.37, 95% CI 1.17–1.61, $p < .001$) and New Zealand (HR 1.28, 95% CI 1.04–1.57, $p = .02$)

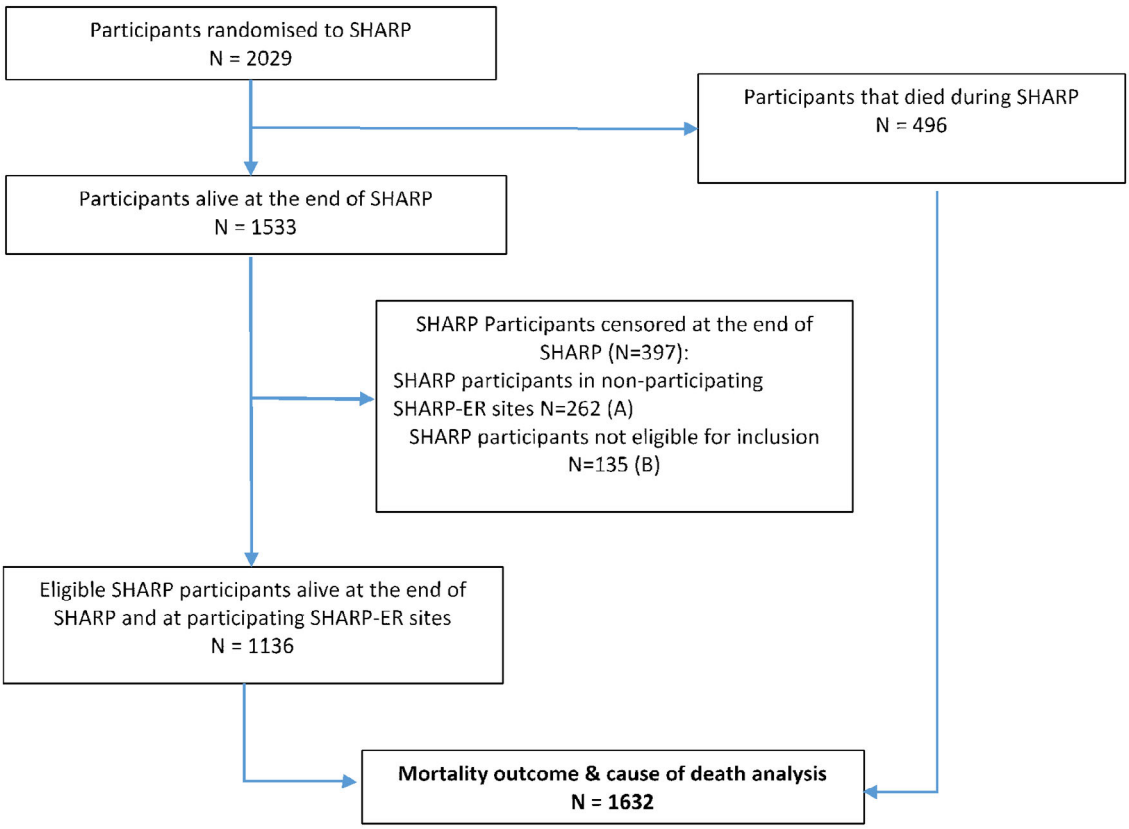

FIGURE 1 Flow diagram of SHARP-ER participants from Australia, Malaysia, and New Zealand. (A) Sites that declined participation in SHARP-ER: 14 sites (262 pts). (B) Participants not eligible for inclusion in SHARP-ER: (135 pts). Declined ($n = 97$), withdrew consent from SHARP ($n = 11$), not found ($n = 12$), other ($n = 15$)

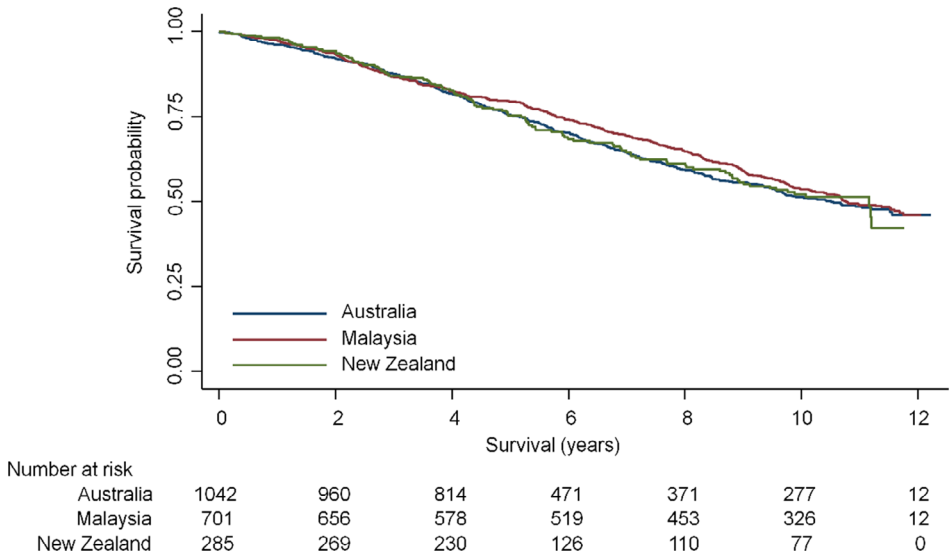

FIGURE 2 Kaplan–Meier survival curves comparing country of enrolment in all study participants using randomization date in SHARP as the start point in survival calculation

when compared to Australian participants as the reference group. More severe CKD at SHARP commencement, with the highest risk seen in participants requiring maintenance dialysis (HR 3.91, 95% CI 3.10–4.94, $p < .001$, stage III CKD as the reference group) and the presence of diabetes (HR 1.81, 95% CI 1.57–2.10, $p < .001$), cerebrovascular disease (1.43, 95% CI 1.03–1.98, $p = .03$) and increasing age (HR 1.06, 95% CI 1.06–1.07, $p < .001$ per yearly increment), were associated with higher mortality.

TABLE 1 Baseline characteristics by country

	Country			
	Australia	Malaysia	New Zealand	Overall
Cohort, *n* (%)	1043 (51)	701 (35)	285 (14)	2029
Age, median (IQR)	65 (54–75)	55 (47–63)	63 (54–70)	61 (50–71)
Sex, *n* (%)				
Male	658 (63)	438 (63)	178 (63)	1274 (63)
Comorbidities, *n* (%)				
Diabetes	224 (22)	200 (29)	53 (19)	477 (24)
Hypertension	883 (85)	614 (88)	228 (80)	1725 (85)
Cerebrovascular disease (CBVD)	42 (4)	9 (1)	13 (5)	64 (3)
Blood pressure, mean (±SD)				
Systolic blood pressure (mm Hg)[a]	140 (±21)	143 (±25)	139 (±22)	141 (±23)
Diastolic blood pressure (mm Hg)[b]	79 (±13)	80 (±12)	80 (±13)	79 (±13)
Estimated glomerular filtration rate, *n* (%)[c]				
30–59 ml/min/1.73 m^2	202 (20)	116 (17)	55 (19)	373 (18)
15–29 ml/min/1.73 m^2	345 (33)	181 (26)	121 (43)	647 (32)
<15 ml/min/1.73 m^2 (non-dialysis)	162 (16)	85 (12)	36 (13)	283 (14)
Dialysis	329 (32)	319 (46)	73 (26)	721 (36)
Albumin to creatinine ratio, *n* (%)[d]				
<30 mg/g	154 (21)	53 (14)	47 (22)	254 (19)
30–300 mg/g	262 (36)	139 (36)	94 (43)	495 (37)
>300 mg/g	315 (43)	193 (50)	78 (36)	586 (44)
Lipid, mean (±SD)[e]				
Total cholesterol (mmol/L)	4.8 (±1.1)	5.0 (±1.1)	4.9 (±1.1)	4.9 (±1.1)
LDL (mmol/L)	2.7 (±0.8)	2.8 (±0.8)	2.8 (±0.8)	2.8 (±0.8)
HDL (mmol/L)	1.1 (±0.3)	1.0 (±0.3)	1.1 (±0.3)	1.0 (±0.3)
Triglycerides (mmol/L)	2.5 (±1.7)	2.7 (±2.0)	2.3 (±1.3)	2.5 (±1.8)
SHARP treatment allocation, *n* (%)[f]				
Simvastatin and ezetimibe	503 (49)	348 (50)	140 (49)	991 (49)
Placebo	524 (50)	353 (50)	145 (51)	1022 (50)

Note: Where presented as *n* (%), this represents the number of participants (as a proportion of participants from each country).
[a]Systolic blood pressure data available for 2026 participants.
[b]Diastolic blood pressure data available for 2025 participants.
[c]Central laboratory creatinine value available for 2024 participants for calculation of Estimated Glomerular Filtration Rate (eGFR) using the Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation.
[d]Urinary albumin to creatinine ratio available for 1335 participants.
[e]Central laboratory lipid profile available for 1941 participants.
[f]Final treatment allocation during SHARP available for 2013 participants.

3.3.3 | Transplantation and competing risk

During data collection 278 participants (14%) received a kidney transplant, with the proportion of transplant recipients differing by country. In Australia, 21% ($n = 214/1043$) of participants received a kidney transplant, compared to 2% ($n = 13/701$) of Malaysian participants and 18% ($n = 51/285$) of participants in New Zealand. Rates of death following transplantation also varied by country; 12% ($n = 26/214$) of Australian participants who were transplanted died during study follow up, compared with 8% ($n = 1/13$) of Malaysian participants and 2% ($n = 1/51$) of participants from New Zealand.

Multivariable competing risk analyses, using the Fine and Gray methodology which treated transplantation as a competing risk for mortality, were consistent with the Cox proportional hazards models, with a higher risk of death in participants from Malaysia (SHR 1.60, 95% CI 1.37–1.89, $p < .001$) and New Zealand (SHR 1.34, 95% CI 1.08–1.65, $p = .01$) when compared to participants enrolled from Australia (Table S4).

TABLE 2 Multivariable Cox regression model to identify the hazard ratios for mortality as a function of country of enrolment

Variable	Hazard ratio	[95% Confidence interval]		$p > \|z\|$
Country				
Malaysia	1.37	1.17	1.61	<.001
New Zealand	1.28	1.04	1.57	.02
eGFR category				
15–29 ml/min/1.73 m^2	1.65	1.30	2.10	<.001
<15 ml/min/1.73 m^2 (non-dialysis)	2.89	2.22	3.75	<.001
Dialysis	3.91	3.10	4.94	<.001
Age (each incremental year)	1.06	1.06	1.07	<.001
Diabetes	1.81	1.57	2.10	<.001
Cerebrovascular disease	1.43	1.03	1.98	.03
Male sex	1.04	0.91	1.19	.58
SHARP treatment (simvastatin and ezetimibe)	*	*	*	*

Note: Australia set as the reference country and eGFR 30–59 ml/min/1.73 m^2 set as the reference eGFR category. The effect of SHARP treatment allocation has not been reported in this analysis pending the broader SHARP PTFU analyses.
Abbreviations: Diabetes, diabetes mellitus; eGFR, estimated glomerular filtration rate.

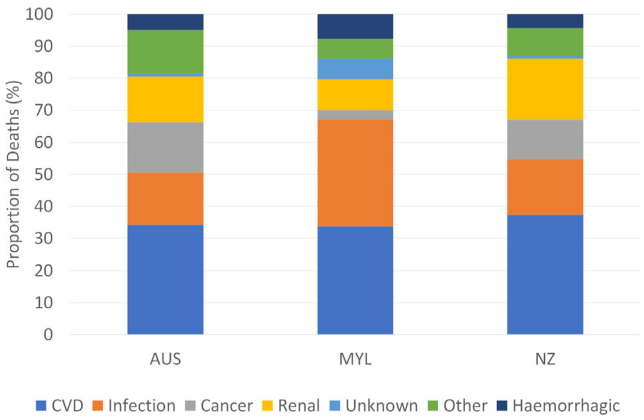

FIGURE 3 A stacked bar chart describing the proportion of deaths attributable to each cause of death by country of enrolment. Each cause of death is presented as a proportion (%) of the total deaths in each country. Definitions: Cardiovascular deaths—included deaths attributed to coronary heart disease, ischaemic or unspecified stroke, cardiac death, vascular death, and sudden death. Renal deaths—included deaths attributed to kidney disease, end stage kidney disease or dialysis withdrawal. Other deaths—included deaths where cause of death was known and attributed to causes other than cardiovascular disease, infection, cancer, renal or haemorrhage. AUS, Australia; CVD, cardiovascular disease; MYL, Malaysia; NZ, New Zealand

3.4 | Secondary outcome—cause of death

The causes of death for participants within each country are shown in Figure 3 and Table S5. Cardiovascular disease (CVD) was the most common cause of death in all countries; accounting for 34% of deaths in Australian participants (n = 144/421), 34% of deaths in Malaysian participants (n = 119/353) and 37% of deaths in New Zealand participants (n = 43/115). An infectious cause of death was more common in Malaysian participants (n = 118/353, 33%) than Australian (n = 69/421, 16%) or New Zealand participants (n = 20/115, 17%), whereas death resulting from cancer was more common in Australian (n = 66/421, 16%) and New Zealand participants (n = 14/115, 12%) than Malaysian (n = 10/353, 3%).

Infectious death was further examined by documented source of infection (Table S6). Respiratory tract infection was the most common source of infectious death in all countries, accounting for 39% of infectious deaths in Australian participants (n = 27/69), 31% of infectious deaths in Malaysian participants (n = 36/118) and 55% of infectious deaths in New Zealand participants (n = 11/20). Dialysis related infection was the second most frequently documented cause of infectious death in all countries (Australia 13% [n = 9/69], Malaysia 18% [n = 21/118], New Zealand 15% [n = 3/20]). An unspecified source of infection was recorded more frequently in Malaysian (n = 39/118, 33%) participants than Australian (n = 20/69, 29%) and New Zealand (n = 2/20, 10%) participants.

4 | DISCUSSION

This study of the extended follow-up of participants enrolled in the SHARP study from Australia, Malaysia and New Zealand has found a higher risk of mortality in participants from Malaysia and New Zealand when compared with participants from Australia. Whilst differences in kidney transplantation rates between the countries is a recognized factor in mortality, adjustment for this did not explain the variation seen between the countries. Cardiovascular disease was the most common cause of death across all three countries, with more infection-related and fewer cancer-related causes of death seen in Malaysia compared to Australia and New Zealand.

International comparisons are important in understanding regional variations in clinical practice and patient outcomes, with a

view to changes in practice improving outcomes. Heterogenous patient characteristics and treatments can, however, confound their interpretation. Analyses of participants enrolled in randomized-controlled trials offers the advantage of standardized eligibility criteria, meaning that participants are more likely to be comparable at baseline. In the case of the SHARP trial, patients were required to have no known history of previous myocardial infarction or coronary revascularisation to be eligible for enrolment. Despite this, there remain important differences in baseline age, severity of CKD and rates of diabetes and cerebrovascular disease between enrolling countries, that likely reflect underlying population and socioeconomic factors. Adjustment for such differences remains important in comparing outcomes between regions.

Marked differences in the rates of transplantation are well recognized across these three countries, especially in relation to Malaysia[10] and were likely to impact upon mortality comparisons. A sensitivity analysis, adjusting for the competing risk of transplantation in the all-cause mortality models,[11,12] revealed little change in the hazard ratios for mortality by country. This would suggest that, in this cohort of patients with advanced CKD, the different transplantation rates (higher in Australia and New Zealand, lower in Malaysia) were not driving the differences in mortality. It may be that transplantation in this selected patient group has a smaller impact upon patient survival, with the observed differences driven by other factors.

The most common cause of death of participants was cardiovascular disease, consistent with previous reports.[13] An infectious cause of death was the second most commonly reported cause of death and was more common in Malaysian participants compared to the other jurisdictions. Whilst this is consistent with the general population in Malaysia, where lower-respiratory infections are the second most prevalent cause of death reported, this is discordant with the general populations in Australia and New Zealand, where deaths from lower-respiratory infections are consistently reported less prevalently.[14] Cancer-associated deaths were less common in participants from Malaysia than from Australia or New Zealand. This is consistent with global health estimates for the general populations of these countries[14] and may also reflect the difference in age of participants enrolled from each country.

This extended analysis has a number of strengths, including the fact that it has follow up of more than two thousand CKD patients from three countries enrolled in the SHARP randomized controlled trial. Robust data collection methods were used for both the SHARP study and the subsequent prospective observational extension study to collect comprehensive information on participants, including linkage to national kidney and mortality registry data. Despite this, several limitations exist. First, recruitment to these studies required participants to fulfil specific eligibility criteria and so the generalisability of our findings to broader CKD populations are unknown. Observational extension studies of randomized controlled trials can also be prone to bias,[15] and whilst we have adjusted for important baseline differences between countries where possible, other unmeasured factors contributing to differences in outcomes may still exist. Second, we have adjusted for the notable difference in rates of transplantation between countries, but have been limited in the ability to explore the impact of other county-level practice differences with a potential impact on mortality, such as use of evidence based therapies and achievement of guideline based treatment targets. Third, around 20% of participants in our study were censored at the completion of SHARP. These participants were mostly from sites that were not able to further participate in the extended follow-up phase (262/397, 66%), however some participants were excluded due to patient infirmity. Whilst this was a minority of participants (135/2029, 7%) this may have implications for the effects seen and the generalisability of our findings.

In conclusion, we have demonstrated a higher risk of mortality in participants from Malaysia and New Zealand when compared with participants from Australia in the extended follow-up of participants enrolled in the SHARP study. Our findings highlight the importance of further research investigating differences in practice patterns in CKD and dialysis care in order to identify where improvements in treatment may be targeted. This study also shows the feasibility and value of the extended follow-up of randomized controlled trials, which has allowed a more nuanced understanding of the differences in mortality risk across the differing participating countries.

AUTHOR CONTRIBUTIONS

Research idea and study design: Benjamin Talbot and Martin Gallagher. Data analysis/interpretation: Benjamin Talbot, Alan Cass, Robert Walker, Lai Hooi, Meg Jardine, Min Jun, Kris Rogers, Louisa Sukkar, Brendan Smyth, and Martin Gallagher. Statistical analysis: Benjamin Talbot, Min Jun, Kris Rogers, and Martin Gallagher. Supervision/mentorship: Martin Gallagher.

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CONFLICT OF INTEREST

Benjamin Talbot is employed as the clinical advisor for Ellen Medical Devices developing the Affordable Dialysis Program. Meg Jardine is responsible for research projects that have received funding from Amgen, Baxter, CSL, Dimerix, Eli Lilly, Gambro, and MSD; has received fees for Advisory, Steering Committee and/or Scientific Presentations from Akebia, Amgen, Astra Zeneca, Baxter, Bayer, Boehringer Ingelheim, Cesas Linx, Chinook, CSL, Janssen, Medscape, MSD, Roche and Vifor; with any consultancy, honoraria or travel support paid to her institution.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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