Drugs & Aging (2018) 35:1005–1015
https://doi.org/10.1007/s40266-018-0582-y

ORIGINAL RESEARCH ARTICLE

# Medication Exposure and Health Outcomes in Older Patients with End-Stage Kidney Disease: A Prospective Study Undertaken in New Zealand

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Published online: 8 September 2018


## Abstract

**Background** The impact of multiple medication exposure on health outcomes among older patients with end-stage kidney disease (ESKD) is unknown.

**Objective** The objective of this study was to identify the impact of medicine exposure on hospitalisation rates and mortality in a prospective longitudinal observational study of older dialysis patients.

**Methods** Patient demographics, medication use, hospitalisation, mortality and co-morbidity data were collected through the prospective longitudinal cohort study DOS65 + (Dialysis Outcomes in those aged ≥ 65 years Study) ($n = 225$). Medication exposure was measured by the total number of individual medications and the number of predetermined 'medication groups'. Associations between medications prescribed at recruitment and health outcomes as measured by hospitalisation and mortality were assessed by univariate and multivariable regression analyses.

**Results** Older ESKD patients were exposed to a median of ten (0–20) medications and eight (0–15) medication groups. Multivariate analyses estimate each additional medication increased mortality risk by 8% (relative risk [RR] = 1.08; 95% confidence interval [CI] 1.07–1.09); each medication group increased mortality risk by 11% (RR = 1.11; 95% CI 1.09–1.12). Similar trends were observed for hospitalisation. Certain medication groups were associated with reduced hospitalisation rates, namely angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (RR = 0.62; 95% CI 0.53–0.72) and dihydropyridines (RR = 0.64; 95% CI 0.54–0.76). Warfarin, gastric acid suppressants, diuretics and β-blockers were associated with increased hospitalisation rates. Warfarin was associated with an increased mortality rate (RR = 1.40; 95% CI 1.19–1.65).

**Conclusions** Multiple medication exposure was prevalent in this older ESKD population, and was associated with an increased risk of mortality and hospitalisation. While this study is not able to determine the cause of these relationships, review of medication use is warranted in this population.

**Trial Registration** ACTRN12611000024943.

## Key Points

There is limited research addressing medication usage and its associations with health outcomes among older end-stage kidney disease (ESKD) patients.

Multiple medication exposure (median of ten medications) was prevalent in this older ESKD population.

Each additional medication was associated with an 8% increase in mortality risk and each medication group increased mortality risk by 11%.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s40266-018-0582-y) contains supplementary material, which is available to authorized users.

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## 1 Introduction

Use of multiple medications, commonly referred to as polypharmacy, can be necessary to achieve evidence-based treatment goals in an aging and increasingly co-morbid population [1]. Polypharmacy has been variously defined according to the number of individual medications, number of classes of medications, or prescribing medications over and above what is clinically indicated [2–5]. Exposure to as few as two and as many as nine medications has been described as polypharmacy, and more than ten is described as 'excessive' polypharmacy [5].

The prevalence of multiple medication use appears to be increasing with age [6], with a median of seven medications in those over the age of 65 years [7, 8], and the highest prevalence (median of 12) among older individuals on dialysis [9]. Medication use is likely to be even greater than reported in the literature as most studies do not include non-prescribed or 'alternative' medicines [6, 10]. Multiple studies have demonstrated an association between medication exposure and increased adverse outcomes in the general older population. For example, polypharmacy has been associated with adverse drug events [11], an increased risk of hospitalisation [2, 12, 13], and an increased risk of death [14, 15]. Whether these associations with adverse outcomes are directly attributable to medication-related toxicity or arise as a consequence of underlying medical complexity is unclear [12]. Patients with chronic kidney disease (CKD) and those on dialysis often have significant co-morbidities [16, 17] and are prescribed multiple medications [8], some of which may be inappropriate, and lead to increased rates of medication-related adverse events [18]. As the number of older people commencing dialysis increases, excess medication exposure is also likely to increase. There is limited research addressing medication usage and its associations with health outcomes among older end-stage kidney disease (ESKD) patients.

Our study aims to (1) describe medication use, and factors impacting on this, in a cohort of ESKD patients aged ≥ 65 years; (2) identify associations between medication use and health outcomes as measured by hospital admission and mortality; and (3) explore which, if any, medication groups are associated with mortality and hospitalisation.

## 2 Methods

Data were collected as part of DOS65 + (Dialysis Outcomes in those aged ≥ 65 years Study), a longitudinal study aiming to assess the quality of life of ESKD patients aged 65 years of age or older. The methods of this study have been detailed elsewhere [19]. Briefly, DOS65 + included 225 consenting participants aged ≥ 65 years, either already on dialysis or eligible for dialysis (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73 $m^2$) who were recruited between January 2011 and May 2014 from three New Zealand District Health Boards (DHBs; Counties Manukau, Southern and Hawkes Bay). All participants were followed prospectively for 3 years, until death or to study end (June 2016). Participants were interviewed at recruitment and again at 1, 2 and 3 years later. Patient demographic data were collected at recruitment, and clinical data were collected at each study timepoint. The study was approved by the New Zealand Multi-Regional Ethics Committee (MEC/10/084) and registered in the Australian New Zealand Clinical Trials Registry (ACTRN12611000024943).

The outcomes of interest were the occurrence of all-cause mortality and hospitalisation over the study period. Mortality and the time to death from recruitment were ascertained using date of death recorded in electronic health records. All-cause hospitalisation was measured as days hospitalised/person/year, excluding day-case admissions as they were assumed to be due to elective procedures. Medications at baseline were recorded by reviewing electronic health records and categorised in two ways: (1) as the number of individual medications; and (2) as the number of predetermined 'medication groups' based on their therapeutic indication. Combination medications containing multiple active ingredients in one formulation were considered as one medication. Medications for obvious short-term use, identified by the dose and frequency prescribed, were excluded. Associations between medication exposure and health outcomes over the follow-up period were then analysed.

Patients' baseline data collected consisted of sex, age (grouped into 65–69, 70–74, 75–79 and > 79 years of age), treating DHB, cause of ESKD and serum albumin (< 35 vs. > 35 g/L) at initial visit. Co-morbidity was recorded as the presence or absence of 26 conditions according to DOPPS (Dialysis Outcomes and Practice Patterns Study) criteria [20]. These co-morbidities were categorized into eight groups, and then dichotomised to 0–2 and ≥ 3 co-morbidities per person. Co-morbidity groups consisted of the presence or absence of: cardiac disease, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, respiratory disease, malignancy (excluding skin cancer), musculoskeletal disease or 'other' co-morbid conditions. Dialysis status was categorised as either haemodialysis (HD), peritoneal dialysis (PD) or 'not on dialysis', then further categorised as centre-based (HD only) or home-based (HD or PD). Number of years on dialysis (dialysis duration) at recruitment was collected from hospital clinical records. Ethnicity was grouped as New Zealand European, Māori

(New Zealand's indigenous population), Asian and Pacific according to Statistics New Zealand Standards [21]. Body mass index (BMI) was derived from clinical record data and grouped using World Health Organization (WHO) categories [22]. Health-related quality of life (HRQoL) at baseline was assessed using the EQ-5D-3L [23], and reported according to the simple summed scores ranging from 5 (no problems with any of the five dimensions) to 15 (extreme problems in all dimensions).

### 2.1 Statistical Analysis

The study sample was described according to demographic, dialysis-related, HRQoL and medication-related characteristics.

Associations between medication exposure and baseline characteristics (demographics, co-morbidity, dialysis-related factors and HRQoL) were assessed using univariate and multivariable Poisson regression analysis to examine co-morbidity and other characteristics as known or potential confounders.

Negative binomial (NB) regression was used to assess univariate associations between medication exposure (number of individual medications and number of medication groups) and hospitalisation rates. Multivariate NB regression was then undertaken to estimate the independent effect of medication exposure adjusted for confounders. Having two measures of medication exposure, as a continuous variable and as a grouped variable, four multivariable models were produced (labelled NB1 to NB4). Similarly, modified Poisson (MP) regression with robust standard errors [24] was used to assess the association between medication exposure and mortality before and after adjusting for confounders. Again, measures of medication exposure were analysed as a continuous variable and as a grouped variable, resulting in four separate models (MP1 to MP4 in Table 5). To account for non-independence by treatment centre, the DHB (i.e. hospital) was used as a cluster variable in all analyses.

Medication groups were then analysed to assess their impact on hospitalisation and mortality, adjusted for confounders. This was done as a two-step process to minimise the possibility of model overfitting due to the small sample size. First, NB and MP models were used to identify medication groups related to hospitalisation and mortality, respectively. A backwards elimination process was used with $p \leq 0.10$ threshold. Results were then adjusted for confounders. Medication groups with very small number of users ($n < 15$) were not included in these analyses. Survival was compared between different levels of medication exposure using Kaplan–Meier plots (Fig. 1). All analyses were completed using STATA® 13.1 software (STATA® Statistical Software: Release 13, 2013; StataCorp, College Station, TX, USA).

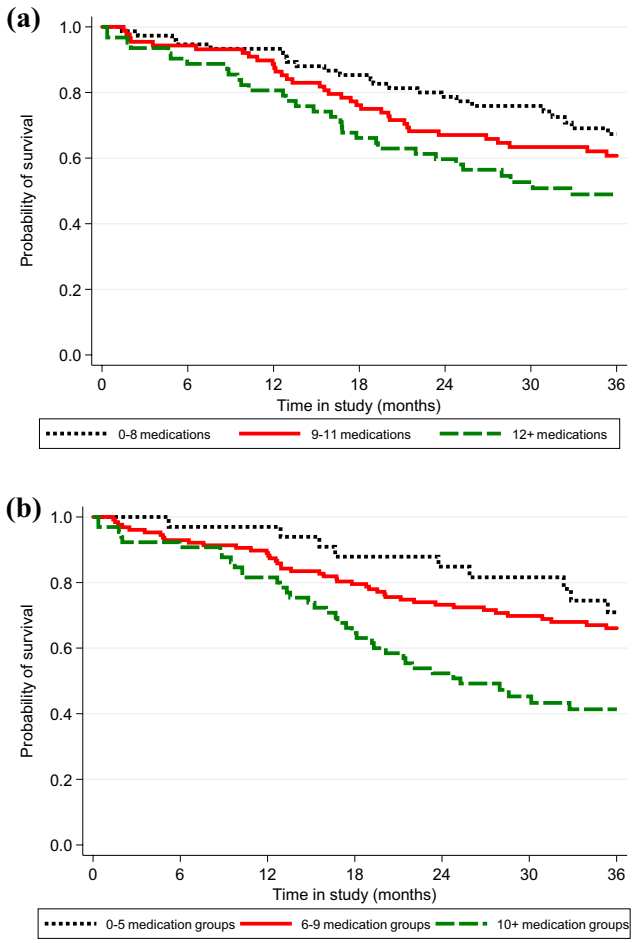


**Fig. 1** Kaplan-Meier survival estimates for different levels of medication exposure by **a** tertiles of individual medications; and **b** tertiles of medication groups

## 3 Results

Of the 225 participants, the majority (64%) were male and were from the Counties Manukau DHB (68%) (Table 1). Māori and Pacific people were over-represented (20% Māori and 24% Pacific) compared with their proportions in the general ≥ 65 years New Zealand population (5% Māori and 2% Pacific) [25]. When compared with the ≥ 65 year New Zealand dialysis population, there were no significant differences in age, sex or dialysis location, but there was a higher proportion of Pacific participants (24% vs. 15%) and a lower proportion of New Zealand Europeans (48% vs. 53%) in our study [26]. Most participants were on dialysis ($n = 169$; 75%); 71 (32%) were dialyzing at home (60 on PD, 11 on HD) and 98 (44%) were dialyzing in centre. The majority of patients (118; 52%) had been dialyzing for 1 year, or more, at baseline, and 51 (23%) had been on dialysis for less than 1 year. The remaining 56 participants (25%) were pre-dialysis stage 5 CKD. The population was highly co-morbid,

**Table 1** Baseline characteristics of the study sample ($n = 225$)

| Characteristic | *n* (%) |
|---|---|
| Age at recruitment (years) | |
| 65–69 | 85 (38) |
| 70–74 | 65 (29) |
| 75–79 | 45 (20) |
| 80–89 | 30 (13) |
| Sex | |
| Male | 144 (64) |
| Female | 81 (36) |
| Ethnicity | |
| European | 108 (48) |
| Māori | 45 (20) |
| Pacific | 53 (24) |
| Asian | 19 (8) |
| BMI (kg/m$^2$) | |
| 18.5–24.9 (normal) | 54 (24) |
| 25.0–29.9 (overweight) | 67 (30) |
| ≥ 30 (obese) | 103 (46) |
| Missing | 1 (0.4) |
| DHB/treatment centre | |
| Counties Manukau | 152 (68) |
| Hawkes Bay | 29 (13) |
| Otago | 44 (20) |
| Co-morbidities | |
| Cardiac disease | 151 (67) |
| Cerebrovascular disease | 17 (8) |
| Peripheral vascular disease | 45 (20) |
| Diabetes mellitus | 120 (53) |
| Lung disease | 49 (22) |
| Cancer (other than skin cancer) | 38 (17) |
| Musculoskeletal | 68 (30) |
| Other co-morbidities | 140 (62) |
| Number of co-morbidities | |
| 0–2 | 104 (46) |
| ≥ 3 | 121 (54) |
| Dialysis duration (years) | |
| 0 to < 1 | 51 (23) |
| 1 to < 3 | 56 (25) |
| 3 to < 6 | 34 (15) |
| 6 to < 9 | 15 (7) |
| ≥ 9 | 13 (6) |
| Dialysis location | |
| Home | 71 (31.6) |
| Centre | 98 (43.6) |
| Not on dialysis | 56 (24.9) |
| Dialysis type | |
| HD | 109 (48.4) |
| PD | 60 (27) |
| Home HD | 11 (0.5) |
| Cause of kidney disease | |
| Glomerulonephritis | 38 (17) |
| Hypertensive vascular | 38 (17) |
| Polycystic | 12 (5) |
| Diabetes | 92 (41) |
| Other | 45 (20) |
| EQ-5D-3L summed score | |
| 5–6 | 81 (36) |
| 7–9 | 118 (52) |
| ≥ 10 | 26 (12) |
| Albumin | |
| High (≥ 36 g/L) | 158 (70) |
| Low (≤ 35 g/L) | 66 (29) |
| Missing | 1 (0.4) |

*BMI* body mass index, *DHB* District Health Board, *HD* haemodialysis, *PD* peritoneal dialysis

having a median of three associated co-morbidities (interquartile range [IQR] = 2–4). The majority of patients had diagnosed cardiac disease (67%) and/or diabetes mellitus (53%). Diabetes mellitus was the most common cause of ESKD (41%) followed by 'other' causes (20%), hypertension (17%) and glomerulonephritis (17%). The EQ-5D-3L summed score had a median of 7 (IQR = 6–8).

The number of individual medications prescribed per patient ranged from two to 20 with a median of ten (IQR = 8–12) and the number of 'medication groups' ranged from two to 15 with a median of eight (IQR = 6–10). Only four (2%) people were prescribed fewer than five individual medications, 75 (33%) were prescribed eight or fewer and 62 (28%) were prescribed 12 or more medications. The majority of participants ($n = 127$; 56%) were prescribed six to nine 'medication groups' with 65 (29%) patients being prescribed ten to 15 medication groups. The most commonly prescribed 'medication groups' were metabolic bone disease-related medications (87%), medication for anaemia management (76%), cholesterol-lowering medications (66%) and antiplatelet agents (65%) (Table 2).

Table 3 presents the univariate analyses for both the individual medication count and 'medication groups'. The number of co-morbidities, serum albumin and a high EQ-5D-3L summed score were associated with increased medication exposure. After accounting for confounders in multivariate Poisson regression, co-morbidities and the EQ-5D-3L maintained associations with increased medication exposure. Each additional co-morbidity was found to account for 0.6 (95% confidence interval [CI] 0.3–0.9) additional medications prescribed.

Hospitalisation rates were highly variable. When split into tertiles by number of individual medications, patients

**Table 2** Medication groups and number of people using them

| Medication group | *n* (%) |
|---|---|
| Analgesics | 58 (26) |
| Antibiotics/antifungals | 6 (3) |
| Anticholinergics | 5 (2) |
| Warfarin | 16 (7) |
| Anticonvulsants | 10 (4) |
| Antidepressants/anxiolytics | 25 (11) |
| Anti-emetics | 2 (1) |
| Antihistamines | 14 (6) |
| Anti-neoplastic agents | 3 (1) |
| Antipsychotics | 3 (1) |
| Antivirals | 4 (2) |
| Asthma/lung disease | 33 (15) |
| Binding resins | 8 (4) |
| ACEI/ARBs | 99 (45) |
| Non-dihydropyridines | 21 (9) |
| Dihydropyridines | 69 (31) |
| β-Blockers | 118 (52) |
| Nitrates | 22 (10) |
| Other cardiovascular medications | 13 (6) |
| Diuretics | 78 (35) |
| Cholesterol management | 148 (66) |
| Anti-platelet agents | 146 (65) |
| Metabolic bone management | 196 (87) |
| Anaemia management | 171 (76) |
| Nutritional supplements (special foods) | 56 (25) |
| Corticosteroids | 18 (8) |
| Diabetic medication | 83 (37) |
| Dietary supplements (vitamins, etc.) | 47 (21) |
| Ophthalmic agents | 3 (1) |
| Uric acid lowering | 93 (41) |
| Immunosuppressants | 7 (3) |
| Laxatives | 69 (31) |
| Agents to manage lower urinary tract symptoms | 31 (14) |
| Gastric prokinetic agents | 9 (4) |
| Gastric acid suppression | 90 (40) |
| Skin creams | 3 (1) |
| Thyroid medications | 15 (7) |
| Other | 31 (14) |

*ACEI* angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blocking agents

prescribed eight or fewer medications spent an average of 12 days in hospital/year (range 0–89), those on nine to 11 medications spent 15 (range 0–99) days in hospital/year, and those on 12 or more medications spent 21 (range 0–84) days in hospital/year. Univariate analyses suggest a tendency towards increased hospitalisation with each additional individual medication (relative risk [RR] 1.07; 95% CI 0.99–1.17) and with each additional medication group (RR 1.12; 95% CI 1.02–1.23) (Table 4). When medication counts and medication groups were analysed as categorical variables by tertiles, there was an increasing risk of hospitalisation across each tertile. Increasing co-morbidity, lower albumin levels (≤35 g/L), increasing dialysis duration and an increasing EQ-5D-3L summed score were all associated with a higher risk of hospitalisation. Neither sex nor age appeared to be related to the risk of hospitalisation. Asian and Māori ethnicity appeared to be associated with a reduced risk of hospitalisation.

Results from four multivariable NB models showing the effect of medication exposure on the risk of hospitalisation after adjusting for a range of possible confounders are shown in Table 2 and summarised in Table 5. When analysed as a continuous variable, each additional medication or medication class was associated with a non-significant increase in the risk of hospitalisation (models NB1 and NB3). When medication count and medication groups were analysed categorically as tertiles, exposure categories were found to be associated with the hospitalisation risk, indicating a dose–response relationship (models NB2 and NB4).

Over the 3 years following recruitment to the study, 88 (39%) participants died. When divided into tertiles of medication use, 31% of those on eight or fewer medications, 39% of those on nine to 11 medications and 50% on more than 11 medications died (Table 4). Univariate analyses of mortality risk found each additional medication or medication group to be associated with an increased risk of death. Age (≥70 years), males, those with more co-morbidities, overweight (but not obese), having a poorer EQ-5D-3L HRQoL and being on dialysis for longer were all independently associated with increased mortality compared with their respective reference categories. People of Māori or Pacific ethnicity appeared to experience a lower risk of death relative to Europeans, while Asian ethnicity appeared to be associated with an increased risk relative to Europeans.

Table 5 summarises the results from four multivariable MP models showing the effect of medication exposure on risk of death after adjusting for confounders. Each additional individual medication (RR 1.08; 95% CI 1.07–1.09) and each medication group (RR 1.11; 95% CI 1.09–1.12) increased the risk of death (models MP1 and MP3, respectively). Compared to those taking eight or fewer individual medications, those using nine to 11 medications (RR 1.23; 95% CI 0.74–2.02), and ≥12 medications (RR 1.55; 95% CI 1.25–1.91) had a higher risk of death (model MP2). Similar relationships were found when medication use was assessed as the number of medication groups (model MP4). (The complete analyses are detailed in Electronic Supplementary Material Tables S1 and S2). Additionally, Kaplan–Meier analyses indicated dose–response relationships between time to death and medication exposure when the latter was considered as tertiles of individual numbers of medications or

**Table 3** Association between medication exposure and baseline characteristics

| Baseline characteristic | Medication count | | | | Medication group count | | | |
|---|---|---|---|---|---|---|---|---|
| | RR | 95% CI[a] | | *p* value[b] | RR | 95% CI[a] | | *p* value[b] |
| Univariate associations | | | | | | | | |
| Co-morbidities | | | | | | | | |
| 0–2 | Ref | | | | Ref | | | |
| ≥ 3 | 1.15 | 1.06 | 1.25 | 0.00 | 1.14 | 1.04 | 1.25 | 0.01 |
| Sex | | | | | | | | |
| Male | Ref | | | | Ref | | | |
| Female | 1.07 | 0.98 | 1.17 | 0.12 | 1.05 | 0.95 | 1.15 | 0.33 |
| Age group (years) | | | | | | | | |
| 65–69 | Ref | | | | Ref | | | |
| 70–74 | 1.04 | 0.94 | 1.15 | | 1.04 | 0.93 | 1.17 | |
| 75–79 | 1.03 | 0.92 | 1.16 | | 1.05 | 0.93 | 1.19 | |
| ≥ 80 | 0.96 | 0.83 | 1.10 | 0.67 | 1.01 | 0.87 | 1.17 | 0.82 |
| BMI (kg/m$^2$) | | | | | | | | |
| 18.5–24.9 | Ref | | | | Ref | | | |
| 25.0–29.9 | 1.01 | 0.90 | 1.13 | | 1.01 | 0.89 | 1.15 | |
| ≥ 30 | 1.06 | 0.96 | 1.18 | 0.41 | 1.05 | 0.93 | 1.18 | 0.66 |
| Ethnicity | | | | | | | | |
| New Zealand European | Ref | | | | Ref | | | |
| Māori | 1.14 | 0.98 | 1.32 | | 1.00 | 0.89 | 1.13 | |
| Pacific | 1.02 | 0.92 | 1.14 | | 1.01 | 0.90 | 1.13 | |
| Asian | 1.01 | 0.91 | 1.12 | 0.41 | 1.09 | 0.92 | 1.29 | 0.79 |
| Albumin | | | | | | | | |
| High (≥ 36 g/L) | Ref | | | | Ref | | | |
| Low (≤ 35 g/L) | 1.10 | 1.01 | 1.21 | 0.03 | 1.09 | 0.99 | 1.20 | 0.09 |
| Dialysis type and location | | | | | | | | |
| PD or HD at home | Ref | | | | Ref | | | |
| HD at centre | 1.01 | 0.90 | 1.13 | | 0.98 | 0.87 | 1.11 | |
| Non-dialysis | 1.04 | 0.94 | 1.16 | 0.67 | 0.97 | 0.86 | 1.09 | 0.86 |
| Dialysis duration (years) | | | | | | | | |
| Non-dialysis | Ref | | | | Ref | | | |
| < 1 | 1.04 | 0.92 | 1.18 | | 1.02 | 0.90 | 1.17 | |
| 1 to < 3 | 0.99 | 0.88 | 1.12 | | 0.95 | 0.84 | 1.09 | |
| 3 to < 6 | 1.09 | 0.96 | 1.25 | | 0.98 | 0.85 | 1.14 | |
| 6 to < 9 | 1.05 | 0.87 | 1.25 | | 0.97 | 0.79 | 1.18 | |
| ≥ 9 | 0.94 | 0.77 | 1.15 | 0.66 | 0.84 | 0.67 | 1.05 | 0.60 |
| EQ-5D-3L summed score | | | | | | | | |
| 5–6 | Ref | | | | Ref | | | |
| 7–9 | 1.14 | 1.04 | 1.24 | | 1.15 | 1.04 | 1.27 | |
| 10–15 | 1.24 | 1.08 | 1.41 | 0.00 | 1.20 | 1.03 | 1.39 | 0.01 |
| Multivariate associations | | | | | | | | |
| Co-morbidities | | | | | | | | |
| 0–2 | Ref | | | | Ref | | | |
| ≥ 3 | 1.12 | 1.03 | 1.23 | 0.01 | 1.13 | 1.03 | 1.24 | 0.01 |
| Albumin | | | | | | | | |
| High (≥ 36 g/L) | Ref | | | | Ref | | | |
| Low (≤ 35 g/L) | 1.09 | 1.00 | 1.19 | 0.06 | 1.08 | 0.98 | 1.20 | 0.13 |
| EQ-5D-3L summed score | | | | | | | | |
| 5–6 | Ref | | | | Ref | | | |
| 7–9 | 1.12 | 1.02 | 1.23 | | 1.13 | 1.02 | 1.25 | |
| 10–15 | 1.16 | 1.01 | 1.33 | 0.03 | 1.14 | 0.97 | 1.33 | 0.05 |

*BMI* body mass index, *CI* confidence interval, *HD* haemodialysis, *PD* peritoneal dialysis, *Ref* reference group, *RR* relative risk

[a]CIs are for the individual category

[b]*p* values are for the whole variable

numbers of medication groups (Fig. 1). Those with increased medication exposure appeared to die sooner.

Multivariate analyses, with adjustments for co-morbidities and other confounders, found that seven medication groups, of the 24 groups used by more than 15 participants (see Table 2), were associated with alterations in the risk of hospitalisation (Table 6). Use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) were associated with a reduced risk of hospitalisation (RR 0.62; 95% CI 0.53–0.72) compared with non-users, as were dihydropyridine calcium channel blockers (RR 0.64; 95% CI 0.54–0.76). Warfarin (RR 1.60; 95% CI 1.26–2.04), dietary supplements (RR 1.23; 95% CI 1.21–1.25), agents suppressing gastric acid production (RR 1.21; 95% CI 1.04–1.39), diuretic agents (RR 1.42; 95% CI 1.13–1.79) and β-blockers (RR 1.24; 95% CI 1.24–1.42) were associated with an increased risk of hospitalisation. Warfarin (RR 1.40; 95% CI 1.19-1.65) and agents to manage metabolic bone disease (RR 1.55; 95% CI 0.99–2.42) were associated with increased risk of mortality while agents used to treat gout (RR 0.8; 95% CI 0.70–0.91) were associated with reduced risk.

## 4 Discussion

Older New Zealanders with ESKD are prescribed a large number of medications. Only four participants (1.7%) were on fewer than five medications. Being prescribed a greater number of medications is associated with an increased risk of hospitalisation and mortality among older New Zealanders with ESKD. This association between medication exposure and adverse outcomes is consistently reported in the general population of older patients [13, 27] but not previously in patients with CKD stage 5 and/or on dialysis.

The most commonly used definition of polypharmacy is the use of five or more medications, which is applicable to 98% of our cohort. Excessive polypharmacy (more than ten medications) occurred in 120 (53%) participants; furthermore, half the participants were prescribed eight or more medication groups. When compared with the New Zealand-wide population over the age of 65 years, participants in this study were much more likely to be prescribed five or more medications than the general older population (98% vs. 29.5%) [8]. In our study, the most commonly prescribed medications were agents to manage metabolic bone disease, anaemia, cardiovascular (including hypertension) disease, dyslipidaemia and conditions requiring antiplatelet therapy, whereas in the older general New Zealand population, the most commonly prescribed agents were laxatives, antihypertensives/antianginals, proton pump inhibitors, antiplatelet agents, bronchodilators and anticoagulants [8]. The observed difference in prescribing pattern appeared to reflect disease-specific management in those with ESKD. Participants in our study were prescribed a similar number of agents to the general dialysis population [18]. When compared with the DOPPS population, there was a markedly higher rate of statin (HMG-CoA reductase inhibitor) use (64% vs. 11.8%) in our study, but similar rates of analgesic, vitamin and antidepressant use [28].

Exposure to multiple medications in general populations is associated with increasing age [10], female sex [10] and non-European ethnicity [8]. None of these factors were associated with increased medication exposure in our study. In this population, number of co-morbidities, HRQoL (EQ-5D-3L) and nutritional status (indirectly assessed by serum albumin) were associated with increased prescribing, as previously observed by Hovstadius and Petersson [10].

Increasing co-morbidity, a low serum albumin and poorer HRQoL may be interpreted as markers of overall poor health status and are associated with increased medication exposure. This suggests that the increased risk of hospitalisation and mortality is at least partly explained by the overall health status. However, the increased risk of hospitalisation and mortality in relation to medication use persists independently, after controlling for these factors. This suggests that increased adverse outcomes could be a direct result of increased medication exposure or could be driven by some unmeasured factors (i.e. residual confounding) causing increased prescribing and associated poorer outcomes. However, our study cannot establish a causal relationship between medication exposure and hospitalisation/mortality. In a study with a shorter follow-up period, which specifically evaluated medication-related problems in dialysis populations, such adverse events were very common (more than four medication-related problems per patient over 2.9 months' follow-up) [18], with 113 documented adverse drug events in 395 patients over this brief follow-up period.

ACEIs/ARBs and dihydropyridine calcium channel antagonists were found to be associated with a lower risk of hospitalisation, whereas warfarin, dietary supplements, gastric acid suppression agents (predominantly proton pump inhibitors), diuretics and β-blockers were associated with an increased hospitalisation risk. Use of uric acid-lowering agents was associated with a lower risk of mortality, while warfarin and metabolic bone medications were associated with an increased mortality risk. DOPPS explored outcomes associated with a limited number of medication groups and found the use of statins and water-soluble vitamins was associated with improved outcomes [28]. This does not appear to be the case in this older population, implying that the findings from younger ESKD populations are poorly generalisable to older populations. Warfarin was the only agent to have consistent associations between the two studies, suggesting

**Table 4** Univariate associations between polypharmacy and other factors with hospitalisation and mortality outcomes

| Characteristic | *n* | Hospitalisation | | | Mortality | | |
|---|---|---|---|---|---|---|---|
| | | Hospitalisation rate (days/person/year) [mean (SD)] | RR | 95% CI | Death [*n* (%)] | RR | 95% CI |
| Individual medication count | | | | | | | |
| Every unit increase | 225 | – | 1.07 | 0.99–1.17 | 88 (39.1) | 1.08 | 1.05–1.11 |
| 0–8 | 75 | 11.9 (16.2) | Ref | | 23 (30.7) | Ref | |
| 9–11 | 88 | 14.8 (19.6) | 1.22 | 1.19–1.25 | 34 (38.6) | 1.26 | 0.80–1.99 |
| 12–20 | 62 | 20.8 (22.6) | 1.74 | 0.96–3.16 | 31 (50.0) | 1.63 | 1.52–1.75 |
| Medication group | | | | | | | |
| Every unit increase | 225 | – | 1.12 | 1.02–1.23 | 88 (39.1) | 1.11 | 1.09–1.13 |
| 0–5 | 33 | 10.3 (13.5) | Ref | | 9 (27.3) | Ref | |
| 6–9 | 127 | 13.2 (18.3) | 1.30 | 1.01–1.66 | 42 (33.1) | 1.21 | 0.84–1.74 |
| 10–15 | 65 | 22.5 (23.1) | 2.20 | 1.48–3.28 | 37 (56.9) | 2.08 | 1.92–2.27 |
| Sex | | | | | | | |
| Male | 144 | 16.0 (19.2) | Ref | | 64 (44.4) | Ref | |
| Female | 81 | 14.5 (20.7) | 0.90 | 0.67–1.21 | 24 (29.6) | 0.67 | 0.54–0.83 |
| Age (years) | | | | | | | |
| 65–69 | 85 | 13.7 (19.5) | Ref | | 21 (24.7) | Ref | |
| 70–74 | 65 | 17.2 (20.7) | 1.25 | 0.64–2.43 | 30 (46.2) | 1.87 | 1.32–2.65 |
| 75–79 | 45 | 14.7 (19.3) | 1.02 | 0.54–1.93 | 20 (44.4) | 1.80 | 1.21–2.68 |
| 80–89 | 30 | 18.0 (19.2) | 1.31 | 0.75–2.27 | 17 (56.7) | 2.29 | 2.02–2.60 |
| BMI ($kg/m^2$) | | | | | | | |
| 18.5–24.9 (normal) | 54 | 15.6 (18.3) | Ref | | 20 (37.0) | Ref | |
| 25.0–29.9 (overweight) | 67 | 17.0 (20.1) | 1.09 | 0.96–1.24 | 28 (41.8) | 1.13 | 1.04–1.23 |
| ≥ 30 (obese) | 103 | 14.5 (20.3) | 0.92 | 0.70–1.19 | 39 (37.9) | 1.02 | 0.80–1.30 |
| Number of co-morbidities | | | | | | | |
| 0–2 | 104 | 10.8 (15.5) | Ref | | 34 (32.7) | Ref | |
| ≥ 3 | 121 | 19.5 (22.0) | 1.87 | 1.32–2.64 | 54 (44.6) | 1.37 | 1.01–1.84 |
| Dialysis status/location | | | | | | | |
| Home (PD or HD) | 71 | 20.7 (21.8) | 1.78 | 0.80–3.99 | 34 (47.9) | 1.58 | 0.88–2.82 |
| Centre (HD) | 98 | 14.0 (20.2) | 1.21 | 0.77–1.91 | 37 (37.8) | 1.24 | 0.84–1.85 |
| Not on dialysis | 56 | 11.4 (14.3) | Ref | | 17 (30.4) | Ref | |
| Dialysis duration | | | | | | | |
| Every unit increase | 225 | – | 1.03 | 1.01–1.05 | 88 (39.1) | 1.04 | 1.00–1.08 |
| Ethnicity | | | | | | | |
| European | 108 | 17.0 (19.7) | Ref | | 46 (42.6) | Ref | |
| Asian | 19 | 9.1 (10.0) | 0.55 | 0.47–0.64 | 10 (52.6) | 1.24 | 1.19–1.28 |
| Māori | 45 | 13.5 (19.8) | 0.81 | 0.67–0.98 | 12 (26.7) | 0.63 | 0.41–0.97 |
| Pacific | 53 | 16.4 (21.9) | 0.96 | 0.83–1.11 | 20 (37.7) | 0.89 | 0.86–0.92 |
| EQ-5D-3L summed score at recruitment | | | | | | | |
| 5–6 | 81 | 11.9 (16.1) | Ref | | 23 (28.4) | Ref | – |
| 7–9 | 118 | 16.4 (19.6) | 1.39 | 1.23–1.57 | 54 (45.8) | 1.61 | 1.32–1.97 |
| 10–15 | 26 | 22.7 (27.4) | 1.93 | 0.80–4.63 | 11 (42.3) | 1.49 | 1.03–2.16 |
| Albumin | | | | | | | |
| High (≥ 36 g/L) | 158 | 13.7 (16.8) | Ref | | 62 (39.2) | Ref | – |
| Low (≤ 35 g/L) | 66 | 19.9 (25.0) | 1.48 | 1.20–1.82 | 26 (39.4) | 1.00 | 0.88–1.15 |

*BMI* body mass index, CI confidence interval, *HD* haemodialysis, *PD* peritoneal dialysis, *Ref* reference group, *RR* relative risk, *SD* standard deviation

**Table 5** Associations between medication exposure and the risks of hospitalisation and death after adjusting for co-morbidities and known confounders

| Measure of medication exposure | Hospitalisation | | | | Mortality | | | |
|---|---|---|---|---|---|---|---|---|
| | Model | RR | 95% CI | *p* value | Model | RR | 95% CI | *p* value |
| Individual medications (continuous count) | | | | | | | | |
| Each unit increase | NB1 | 1.04 | 0.95–1.13 | 0.39 | MP1 | 1.08 | 1.07–1.09 | <0.01 |
| Individual medications (grouped count) | | | | | | | | |
| 0–8 | NB2 | Ref | | | MP2 | Ref | | |
| 9–11 | | 1.07 | 0.99–1.16 | | | 1.23 | 0.74–2.02 | |
| 12–20 | | 1.33 | 0.64–2.75 | <0.01 | | 1.55 | 1.25–1.91 | <0.01 |
| Medication types (continuous count) | | | | | | | | |
| Each unit increase | NB3 | 1.09 | 0.99–1.20 | 0.08 | MP3 | 1.11 | 1.09–1.12 | <0.01 |
| Medication types (grouped count) | | | | | | | | |
| 0–5 | NB4 | Ref | | | MP4 | Ref | | |
| 6–9 | | 1.26 | 0.98–1.63 | | | 1.22 | 0.80–1.86 | |
| 10–15 | | 1.96 | 1.11–3.45 | <0.01 | | 2.12 | 2.07–2.17 | <0.01 |

Medication exposure was measured by the count of individual medications in NB1, NB2, MP1 and MP2 models, and by the count of medication groups in NB3, NB4, MP3 and MP4 models. Those exposure measures were used as continuous variables in NB1, NB3, MP1, and MP3 models, and as categorical variables in NB2, NB4, MP2, and MP4 models. CIs are for individual categories while *p*-values are for the whole variable. All RRs are adjusted for sex, age, body mass index, ethnicity, co-morbidities, albumin, dialysis location, dialysis duration and EQ-5D-3L score

*CI* confidence interval, *MP* modified Poisson, *NB* negative binomial, *Ref* reference category, *RR* relative risk

**Table 6** Medication groups associated with hospitalisation rate and mortality

| Medication group | RR | 95% CI | *p* value |
|---|---|---|---|
| Hospitalisation rate | | | |
| Warfarin | 1.60 | 1.26–2.04 | <0.01 |
| Dietary | 1.23 | 1.21–1.25 | <0.01 |
| Gastric acid suppression | 1.21 | 1.04–1.39 | 0.01 |
| Diuretics | 1.42 | 1.13–1.79 | <0.01 |
| β-Blockers | 1.24 | 1.09–1.42 | <0.01 |
| ACEi/ARB | 0.62 | 0.53–0.72 | 0.01 |
| Dihydropyridines | 0.64 | 0.54–0.76 | <0.01 |
| Mortality | | | |
| Warfarin | 1.40 | 1.19–1.65 | <0.01 |
| Metabolic bone | 1.55 | 0.99–2.42 | 0.06 |
| Gout | 0.80 | 0.70–0.91 | <0.01 |

Associations were adjusted for age, dialysis type (haemodialysis/peritoneal dialysis vs. not), co-morbidities, albumin level, medication groups count and ethnicity

*ACEi* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CI* confidence interval, *RR* relative risk

adverse outcomes associated with these agents are likely to be generalisable to patients on dialysis irrespective of age. A patient being prescribed agents to attempt to control metabolic bone disease is likely to represent an indirect marker of poor overall health status and the association with mortality may reflect this. In New Zealand, as a result of funding regulations, the most commonly prescribed phosphate binders are calcium-containing agents. Calcium-containing phosphate binders have been observed to be associated with increased cardiovascular events and mortality when compared with non-calcium-containing agents [29]. This may be an explanation for the excess mortality observed in this study. We are not able to generate a plausible explanation for the association between allopurinol and a reduction in mortality.

A number of tools have been developed to facilitate the de-prescribing of medications for older non-ESKD patients. When applied, these tools have been shown to reduce mortality, improve health perception, reduce pharmaceutical cost and reduce referral to nursing homes [30–33]. A tool specifically aimed at de-prescribing in patients on dialysis was developed recently [9]. Using this tool, targeting a small number of medications (quinine, diuretics, α-blockers, proton pump inhibitors and statins), a modest reduction in medication exposure was achieved without evidence of harm from under-treatment. While patients with ESKD are likely to be prescribed multiple agents due to complications related to the disease process, in our population patients were frequently prescribed medications with questionable efficacy. Two-thirds of our study population were prescribed statins, despite randomized controlled trials and a subsequent Cochrane Review [34] failing to demonstrate benefit of statins for people undergoing dialysis. Actively de-prescribing these and other agents with questionable efficacy is unlikely to result in under-treating harm and may result in improved health outcomes. Additionally, reducing

medication burden is likely to improve adherence to remaining medications with clear indications and resultant benefit [33].

Strengths of this study include the prospective design, explicit focus on older ESKD patients and having no participants lost to follow-up. All New Zealanders with ESKD are treated in a publicly funded universal-access health system where there are no (or limited) socioeconomic barriers to accessing nephrology treatment for ESKD. The study also used two health outcomes, medication exposure was measured in two main ways and different methods were used to explore the consistency in findings. Excess medication exposure was not arbitrarily defined; rather, it was analysed as both continuous and categorical variables. Results were adjusted for a range of possible confounders. Almost all data were medically validated as sourced from medical records rather than relying on participant self-reporting.

Limitations of this study relate to the small number of participants, which restricted the number of variables able to be included in the multivariable model, and hence there may have been insufficient power to detect certain associations where these may exist. We were unable to account for either non-adherence to prescribed medications or non-prescription medications. Medication exposure was measured only at a single timepoint, at time of recruitment into the study. Lastly, analyses assumed each co-morbidity, analysed as counts, had the same influence on the outcomes of interest.

## 5 Conclusions

This prospective study demonstrated that older stage 5 CKD patients were prescribed a large number of medications influenced by co-morbidity burden, nutritional status and reduced HRQoL. Increased medication exposure was associated with an increased risk of mortality and of hospitalisation. Some medication groups were association with reduced hospitalisation or mortality, whilst other medications were associated with an increased risk of mortality or hospitalisation.

**Acknowledgements** Sashika Samaranayaka was a recipient of an Otago Medical Research Foundation–Metro Realty summer studentship.

**Author Contributions** RW and SD were responsible for the research idea and design; all authors contributed to data analyses and interpretation, manuscript authorship and review; AS and SS were responsible for the statistical analyses. SS was supervised by RW, SD, JS and AS.

### Compliance with Ethical Standards

**Funding** The DOS65 + (Dialysis Outcomes in those aged ≥ 65 years Study) was funded by the Health Research Council (HRC) of New Zealand (HRC 10/354). The study was investigator-initiated and analysed, with no contribution from the HRC to the analyses.

**Conflict of interest** Sashika Samaranayaka, Robert Walker, Ari Samaranayaka, Sarah Derrett and John Schollum declare that they have no conflicts of interest relevant to the content of this study.

**Ethical approval** The study was approved by the New Zealand Multi-Regional Ethics Committee (MEC/10/084) and registered in Australian New Zealand clinical trials registry (ACTRN12611000024943).

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