

Impact of Polypharmacy on Health-Related Quality of Life in Dialysis Patients

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Keywords

Polypharmacy · Health-related quality of life · Quality of life · Dialysis

Abstract

Introduction: Dialysis patients are often prescribed a large number of medications to improve metabolic control and manage coexisting comorbidities. However, some studies suggest that a large number of medications could also detrimentally affect patients' health-related quality of life (HRQoL). Therefore, this study aims to provide insight in the association between the number of types of medications and HRQoL in dialysis patients. **Methods:** A multicentre cohort study was conducted among dialysis patients from Dutch dialysis centres 3 months after initiation of dialysis as part of the ongoing prospective DOMESTICO study. The number of types of medications, defined as the number of concomitantly prescribed types of drugs, was obtained from electronic patient records. Primary outcome was HRQoL measured with the Physical Component Summary (PCS) score and Mental Component Summary (MCS) score (range 0–100) of the Short Form 12. Secondary outcomes were number of symptoms (range 0–30) measured with the Dialy-

sis Symptoms Index and self-rated health (range 0–100) measured with the EuroQol-5D-5L. Data were analysed using linear regression and adjusted for possible confounders, including comorbidity. Analyses for MCS and number of symptoms were performed after categorizing patients in tertiles according to their number of medications because assumptions of linearity were violated for these outcomes. **Results:** A total of 162 patients were included. Mean age of patients was 58 ± 17 years, 35% were female, and 80% underwent haemodialysis. The mean number of medications was 12.2 ± 4.5 . Mean PCS and MCS were 36.6 ± 10.2 and 46.8 ± 10.0 , respectively. The mean number of symptoms was 12.3 ± 6.9 and the mean self-rated health 60.1 ± 20.6 . In adjusted analyses, PCS was 0.6 point lower for each additional medication (95% confidence interval [95% CI]: -0.9 to -0.2 ; $p = 0.002$). MCS was 4.9 point lower (95% CI: -8.8 to -1.0 ; $p = 0.01$) and 1.0 point lower (95% CI: -5.1 – -3.1 ; $p = 0.63$) for the highest and middle tertiles of medications, respectively, than for the lowest tertile. Patients in the highest tertile of medications reported 4.1 more symptoms than in the lowest tertile (95% CI: 1.5–6.6; $p = 0.002$), but no significant difference in the number of symptoms was observed between the middle and lowest tertiles. Self-rated health was 1.5 point lower for each medication (95% CI: -2.2 to -0.7 ; p

< 0.001). **Discussion/Conclusion:** After adjustment for comorbidity and other confounders, a higher number of medications were associated with a lower PCS, MCS, and self-rated health in dialysis patients and with more symptoms.

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Introduction

Patients with end-stage kidney disease who undergo dialysis report a significantly lower health-related quality of life (HRQoL) than the general population [1]. Moreover, their HRQoL is worse than the HRQoL of kidney transplant recipients and patients with other chronic diseases such as diabetes, congestive heart failure, malignancies, and chronic lung disease [1, 2].

Several factors could contribute to this diminished HRQoL of dialysis patients. First, dialysis patients commonly suffer from numerous somatic and mental health-related symptoms attributable to kidney failure or kidney failure-related comorbidity such as dyspnoea, pruritus, fatigue, sleeping disorders, anxiety, and depression [3, 4]. Second, stringent dietary and other lifestyle restrictions to prevent accumulation of fluid and electrolytes and to improve metabolic control can also diminish HRQoL [5].

In addition, dialysis treatment itself can detrimentally affect patients' HRQoL. First, dialysis severely restricts patients' freedom since multiple dialysis sessions per week usually are required to sufficiently compensate a loss of kidney function. Second, dialysis-related complications such as infections or problems with dialysis access can arise which require hospitalization or additional treatment [6, 7]. Third, patients undergoing haemodialysis frequently suffer from intradialytic and post-dialytic symptoms such as fatigue, hypotension, and muscle cramps [8].

Studies in various patient populations, including kidney transplant recipients and geriatric patients, suggest that polypharmacy can also negatively affect HRQoL [9, 10]. This may be due to complexity of medication regimens and medication-related problems such as adverse events [11–13]. Exposure to polypharmacy seems unavoidable for dialysis patients since they invariably require multiple medications to treat the course of kidney failure and coexisting comorbidity and to correct ensuing metabolic disturbances [14, 15].

Despite this consequent exposure to polypharmacy among dialysis patients, only a handful of studies to date have evaluated the association between polypharmacy and HRQoL in this patient population, of which only one

study particularly focussed on polypharmacy and HRQoL [16–18]. Therefore, the primary aim of this study is to explore the association between the number of types of medication and HRQoL in dialysis patients.

Materials and Methods

Study Design

We conducted a cross-sectional multicentre cohort study among dialysis patients as part of the ongoing prospective Dutch nocturnal and home dialysis Study To Improve Clinical Outcomes (DOMESTICO) [19]. DOMESTICO is a prospective international cohort study in the Netherlands and Belgium that longitudinally compares HRQoL and clinical outcomes of home dialysis and in-centre haemodialysis patients. For the present study, we used medication and HRQoL data at 3 months after the start of dialysis. Patients are eligible to be included in DOMESTICO if they are at least 18 years old and diagnosed with end-stage kidney disease for which they have to (re)start with haemodialysis or peritoneal dialysis. Exclusion criteria are a life expectancy shorter than 3 months and an expected kidney transplant within 3 months [19]. Patients have been included in DOMESTICO from December 2017 onwards.

Study Population

The study population consisted of a subset of DOMESTICO patients at 3 months after dialysis initiation from 7 Dutch dialysis centres: 4 university hospitals, 2 community hospitals, and 1 stand-alone dialysis centre. Participating centres were selected based on the availability of complete data on patients' prescribed medication. Patients were screened for inclusion until July 2020. Additional exclusion criteria for this study were no available medication list at 3 months or a missing Short Form 12 (SF-12), which is the primary outcome. Patients were secondarily excluded if they had filled out less than 75% of the SF-12.

Medication Measurements

Medication data were retrieved from patients' electronic patient files. The number of medications was defined as the number of concomitantly prescribed types of drugs. All medication that was prescribed for at least 14 consecutive days was listed, including prescribed-as-needed and non-systemic medication. Drugs from the same pharmacological subgroup, for example, insulin glargine and insulin aspart, were counted as separate medications. Single-pill combinations were counted as the number of drugs included (for example, lisinopril/hydrochlorothiazide was considered as 2 types of medication) for 2 reasons: first, single-pill combinations consist of multiple medications that each have their own pharmacodynamics that can affect HRQoL. Counting these medications as separate medications fits our study objective best as we investigate the association between the number of types of prescribed medications, and HRQoL rather than daily pill burden. Furthermore, in The Netherlands, it depends on the prescribing physician and pharmacy if medication is dispensed to patients as separate medications or in a combination medication. Including single-pill combinations as the number of included drugs ensures that all medication is weighed equally irrespective of the prescribing physician's and pharmacist's decision to prescribe medication as a sin-

gle-pill combination or as separate medications. Over-the-counter drugs and herbal medicines were excluded to avoid misclassification bias [20]. Medications administered during dialysis were also excluded. Polypharmacy was defined as the concurrent prescription of 5 or more types of medication [21].

HRQoL Measurement

HRQoL was assessed using 3 self-reported questionnaires, which have been validated for dialysis patients [22, 23]: the SF-12, the Dialysis Symptom Index (DSI), and the EuroQoL-5D-5L (EQ-5D-5L). The SF-12 and EQ-5D-5L are generic quality of life questionnaires, and the DSI is a dialysis-specific questionnaire. Patients filled out questionnaires online or on paper, depending on their preference. If patients' 3-month questionnaire was missing, their 6-month questionnaire was used as a substitute.

The primary outcome was HRQoL measured with the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores of the SF-12 [24]. The SF-12 is a condensed version of the Short Form 36 comprising 12 of its items from which PCS and MCS scores are calculated [25]. Scores were standardized to US general population scores with a mean of 50 and a standard deviation of 10. Scores range from 0 to 100 with higher scores indicating better HRQoL. A difference of 3 points in SF-12 summary scores was considered clinically important [26, 27].

Secondary HRQoL outcomes were the number of symptoms and total symptom burden measured with the DSI and EQ-5D-5L utility score and self-rated health measured with the EQ-5D-5L. The DSI assesses the prevalence and severity of 30 dialysis-related symptoms [28]. Patients indicate per symptom whether they experienced it during the past week and, if so, its severity on a 5-point Likert scale ranging from 1 ("not at all bothersome") to 5 ("very bothersome"). The number of symptoms (range 0–30) is the number of times a patient answered "yes" to an item. The total symptom burden (range 0–150) is the sum of the Likert scale scores. Higher scores indicate a higher symptom burden.

The EQ-5D-5L rates patients' HRQoL on 5 domains [29]. Each domain is scored on a 5-point Likert scale from which utility scores were calculated using the Dutch value set (range 0–1) [30]. In addition, the EQ-5D-5L measures patients' self-rated health on a visual analogue scale (range 0–100). Higher scores indicate better HRQoL and self-rated health.

Collection of Covariates

Patient demographics, medical history, and clinical parameters were collected from electronic patient files and questionnaires. Cause of kidney failure was categorized based on the classification of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) [31]. Comorbidity scores were calculated using the Charlson Comorbidity Index (CCI), which includes the presence and severity of a wide range of conditions [32].

Statistical Analyses

Categorical variables are presented as percentages and continuous variables as mean \pm standard deviation (SD) or median and interquartile range, depending on whether they are normally distributed. The association between the number of medications and HRQoL was analysed using linear regression. Assumptions of linearity were violated for MCS score, number of symptoms, total symptom burden, and EQ-5D-5L utility scores. These outcomes

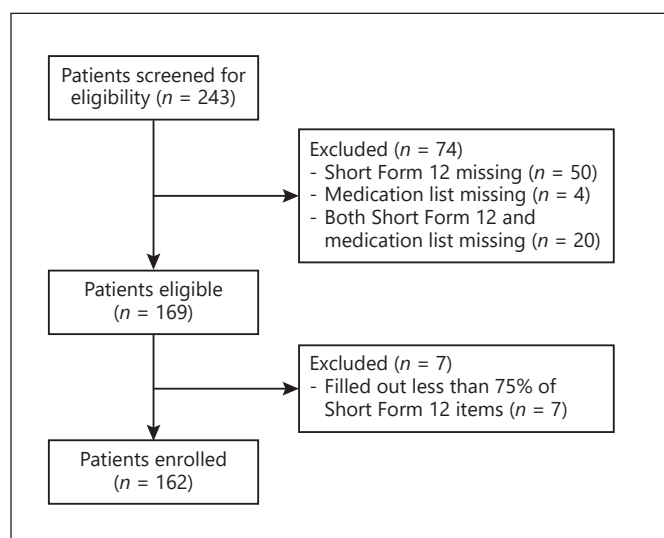


Fig. 1. Flowchart of patient selection.

were therefore analysed after categorizing patients in tertiles of medications as using existing classifications of polypharmacy would have resulted in significantly unequal groups. Patient characteristics across different tertiles were compared using analysis of variance, Kruskal-Wallis test, or χ^2 test.

Adjustment for confounding was based on 2 models: model 1 was adjusted for age and sex and model 2 was further adjusted for comorbidity according to CCI, dialysis modality, acute start of dialysis, and hospitalization in the past 3 months. Outcomes were considered statistically significant for $p \leq 0.05$.

Missing data were imputed using multiple imputation techniques. Twenty imputed datasets were created through predictive mean matching. Missing data in questionnaires were imputed at item level instead of score level from which total scores were calculated [33]. Multiple imputation was not conducted for questionnaires which missed more than 25% of questionnaire items.

Sensitivity Analyses

To further explore the robustness of our results, 2 sensitivity analyses were performed for both crude and adjusted analyses. The impact of multiple imputation was investigated by conducting an analysis of patients with complete questionnaires (complete case analysis). The impact of using 6-month questionnaires was investigated by including only patients with a 3-month questionnaire. All data were analysed in SPSS (version 26.0).

Results

Patient Selection

In total, 243 patients were screened for eligibility, of whom 162 were included (Fig. 1). Main reasons for exclusion were missing SF-12 ($n = 50$) or missing SF-12 and medication list ($n = 20$) (Fig. 1).

Table 1. Patient characteristics for all patients and per medication tertile

	All patients (<i>n</i> = 162)	2–10 medications (<i>n</i> = 59)	11–13 medications (<i>n</i> = 42)	14–27 medications (<i>n</i> = 61)
Demographic data				
Age, years	58±17	55±19	62±15	59±14
Sex (female)	56 (35)	22 (37)	12 (29)	22 (36)
Medical history				
Cause of kidney failure ^a				
Glomerular/tubular nephropathy	38 (24)	12 (20)	10 (24)	16 (26)
Cystic kidney disease	15 (9)	10 (17)	2 (5)	3 (5)
Renovascular nephropathy	44 (27)	15 (25)	15 (36)	14 (23)
Diabetic nephropathy	26 (16)	3 (5)	8 (19)	15 (25)
Other/unknown	39 (24)	19 (32)	7 (17)	13 (21)
Previous dialysis	20 (12)	4 (7)	7 (17)	9 (15)
Dialysis vintage ^b (months)	32.5 (11.8–64.3)	32.0 (8.3–64.0)	21.0 (7.0–67.0)	51.0 (18.0–77.5)
Previous kidney transplant	37 (23)	10 (17)	11 (26)	16 (26)
Charlson comorbidity index	3.0 (2.0–5.0)	2.0 (2.0–3.0)	4.0 (2.0–5.0)	4.0 (2.0–5.5)
Hospitalization in the past 3 months	60 (39)	15 (27)	19 (46)	26 (46)
Current dialysis				
Dialysis modality				
Haemodialysis	130 (80)	49 (83)	34 (81)	47 (77)
Peritoneal dialysis	32 (20)	10 (17)	8 (19)	14 (23)
Acute start of dialysis	23 (14)	14 (24)	4 (10)	5 (8)
Clinical parameters				
BMI, kg/m ²	26.6±6.4	26.5±6.6	26.2±5.5	26.8±6.9
Residual diuresis ^c	141 (97)	51 (100)	38 (100)	52 (93)
Haemoglobin, mmol/L	6.8±1.0	6.9±1.2	6.9±1.0	6.8±0.9
Phosphate, mmol/L	1.73±0.53	1.79±0.55	1.68±0.50	1.72±0.54
Calcium, mmol/L	2.26±0.21	2.27±0.18	2.31±0.15	2.22±0.25
Albumin, g/L	37.5±6.4	38.5±5.0	37.2±5.5	36.8±8.0
Medication use				
Medications (mean), <i>n</i>	12.2±4.5	7.6±2.0	12.0±0.9	16.7±2.9
Medications (median), <i>n</i>	12 [9–15]	8 [6–9]	12 [11–13]	16 [14–19]
Polypharmacy ^d	158 (98)	55 (93)	42 (100)	61 (100)
Health-related quality of life				
SF-12 PCS	36.6±10.2	40.2±10.9	36.8±9.8	33.2±8.9
SF-12 MCS	46.8±10.0	49.1±9.1	47.8±10.2	44.1±10.3
Symptoms, <i>n</i>	12.3±6.9	11.0±6.3	9.7±6.6	15.5±6.7
Symptom burden	33.2±21.9	29.7±19.4	23.8±19.0	43.2±22.9
EQ-5D-5L utility score	0.71±0.24	0.80±0.18	0.75±0.23	0.61±0.27
Self-rated health	60.1±20.6	66.7±18.4	62.2±20.5	52.1±20.2

Continuous variables are presented as mean±standard deviation or median [interquartile range] and categorical variables as *n* (%). The sum of percentages may not equal 100 due to rounding off to the nearest integer. Reported values are from the non-imputed dataset. Missing data: BMI was missing for 22 participants (14%), residual diuresis for 17 (10%), albumin for 10 (6%), hospitalization in the past 3 months for 8 (5%), haemoglobin and phosphorus for 7 (4%), and calcium for 6 (4%). Other variables contained no missing data. SF-12 was complete for 139 patients (86%), DSI for 121 (75%), and EQ-5D-5L for 150 (93%). BMI, body mass index; SF-12, Short Form 12; PCS, Physical Component Summary score; MCS, Mental Component Summary score; EQ-5D-5L, EuroQoL-5D-5L. ^aBased on ERA-EDTA codes. ^bOnly for patients who have previously undergone dialysis. ^cDefined as the urine production >100 mL/day. ^dDefined as the concurrent use of 5 or more medications.

Patient Characteristics

Patient characteristics are listed in Table 1. Mean age was 58 ± 17 years, 56 patients (35%) were female, 130 (80%) underwent haemodialysis, and 32 (20%) peritoneal dialysis. The mean number of medications was 12.2 ±

4.5 (range 2–27), and 158 patients (98%) met the criteria for polypharmacy. Categorizing patients in tertiles resulted in tertiles in which the number of medications ranged from 2 to 10 (mean 7.6), 11 to 13 (mean 12.0), and 14 to 27 (mean 16.7). Patients with 11–13 and 14–27 medica-

Table 2. Association between the number of types of medication and HRQoL

	Unadjusted		Model 1 ^a		Model 2 ^b	
	RC (95% CI)	<i>p</i> value	RC (95% CI)	<i>p</i> value	RC (95% CI)	<i>p</i> value
Short Form 12						
PCS	-0.7 (-1.0 to -0.4)	<0.001	-0.7 (-1.0 to -0.3)	<0.001	-0.6 (-0.9 to -0.2)	0.002
MCS ^c						
2–10 types of medications	REF		REF		REF	
11–13 types of medications	-0.6 (-4.5–3.4)	0.77	-1.0 (-5.1–3.0)	0.62	-1.0 (-5.1–3.1)	0.63
14–27 types of medications	-4.1 (-7.7 to -0.6)	0.02	-4.3 (-7.9 to -0.7)	0.02	-4.9 (-8.8 to -1.0)	0.01
Dialysis symptom index						
Symptoms, <i>n</i> ^c						
2–10 types of medications	REF		REF		REF	
11–13 types of medications	-1.3 (-3.8–1.3)	0.32	-0.9 (-3.5–1.7)	0.49	-1.2 (-3.9–1.5)	0.37
14–27 types of medications	4.4 (2.2–6.7)	<0.001	4.6 (2.3–6.8)	<0.001	4.1 (1.5–6.6)	0.002
Total symptom burden ^c						
2–10 types of medications	REF		REF		REF	
11–13 types of medications	-1.7 (-9.7–6.2)	0.67	-0.4 (-8.4–7.7)	0.92	-1.9 (-10.3–6.5)	0.66
14–27 types of medications	16.8 (9.7–23.9)	<0.001	17.3 (10.2–24.4)	<0.001	14.8 (6.9–22.7)	<0.001
EuroQoL-5D-5L						
EQ-5D-5L utility score ^c						
2–10 types of medications	REF		REF		REF	
11–13 types of medications	-0.05 (-0.14–0.05)	0.32	-0.06 (-0.15–0.04)	0.24	-0.05 (-0.15–0.05)	0.31
14–27 types of medications	-0.20 (-0.28 to -0.12)	<0.001	-0.20 (-0.29 to -0.12)	<0.001	-0.19 (-0.28 to -0.09)	<0.001
Self-rated health	-1.6 (-2.3 to -1.0)	<0.001	-1.7 (-2.4 to -1.0)	<0.001	-1.5 (-2.2 to -0.7)	<0.001

Two patients were omitted from the DSI analyses and 4 from the EQ-5D-5L analyses because they missed more than 25% of items. RC, regression coefficient; REF, reference category; PCS, Physical Component Summary Score; MCS, Mental Component Summary score; EQ-5D-5L, EuroQoL-5D-5L. ^a Model 1: adjusted for age and sex. ^b Model 2: further adjusted for Charlson Comorbidity Index, dialysis modality, acute start of dialysis, and hospitalization in the past 3 months. ^c Analysed with a number of medications categorized in tertiles due to violation assumptions of linearity.

tions had a higher CCI and a higher prevalence of diabetic nephropathy than patients with 2–10 medications. The prevalence of cystic kidney disease and acute start of dialysis was higher among patients with 2–10 medications than patients with 11–13 and 14–27 medications.

HRQoL Scores

Patients' HRQoL scores are listed in Table 2. The SF-12 was filled out completely for 139 patients (86%), the DSI for 121 (75%), and the EQ-5D-5L for 151 (93%). Six-month instead of 3-month questionnaires were used for 22 patients. Mean PCS and MCS scores were 36.6 ± 10.2 and 46.8 ± 10.0 , respectively. Mean number of symptoms was 12.3 ± 6.9 and mean symptom burden 33.2 ± 21.9 . Mean EQ-5D-5L utility score was 0.71 ± 0.24 and mean self-rated health 60.1 ± 20.6 . Mean PCS and MCS scores, EQ-5D-5L utility score, and self-rated health were lower for subsequent tertiles. Mean number of symptoms and total symptom burden were highest for patients with 14–27 medications and lowest for patients with 11–13 medications.

Association between the Number of Types of Medication and HRQoL

The results of the analyses are illustrated in Figure 2 and summarized in Table 2. Results of the crude and adjusted analyses were comparable. In the adjusted analyses, PCS score was 0.6 point (95% confidence interval [95% CI]: -0.9 to -0.2) lower for each additional medication. MCS score was 4.9 (95% CI: -8.8 to -1.0) and 1.0 point (95% CI: -5.1 to -3.1) lower for patients with 14–27 and 11–13 medications, respectively, than patients with 2–10 medications. In addition, patients with 14–27 medications reported 4.1 more symptoms (95% CI: 1.5–6.6) and a 14.8 point higher total symptom burden (95% CI: 6.9–22.7) than patients with 2–10 medications. Patients with 14–27 medications also reported 0.19 (95% CI: -0.28 to -0.09) point lower EQ-5D-5L utility scores than patients with 2–10 medications. Self-rated health was 1.5 point lower (95% CI: -2.2 to -0.7) for each additional medication. No statistically significant difference was observed in the number of symptoms, total symptom burden, and EQ-5D-5L utility score between patients with 11–13 and 2–10 medications.

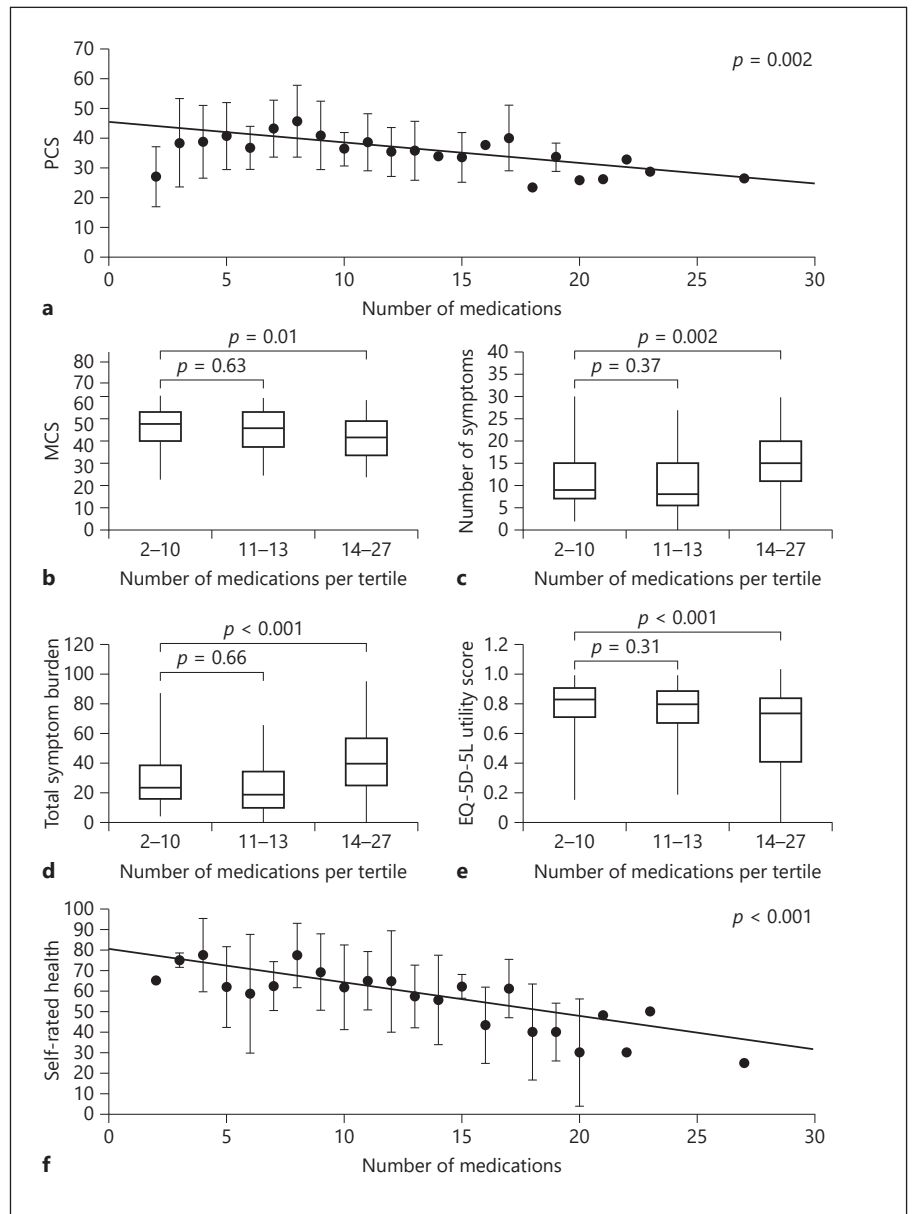


Fig. 2. PCS scores (a), MCS scores (b), number of symptoms (c), total symptom burden (d), EQ-5D-5L utility score (e), and self-rated health (f) per number of medications for adjusted analyses. PCS, Physical Component Summary; MCS, Mental Component Summary; EQ-5D-5L, EuroQoL-5D-5L.

Sensitivity Analyses

Results for the sensitivity analyses were comparable to the result from the main analyses apart from total symptom burden in the complete case analysis. In this adjusted analysis, a smaller difference in total symptom burden was observed for patients with 14–27 medications (difference 9.1 95% CI: –0.8–19.1) and a larger difference for patients with 11–13 medications (difference –7.4 95% CI: –17.5–2.8) than patients with 2–10 medications, respectively (online suppl. Table 1; see www.karger.com/doi/10.1159/000518454 for all online suppl. material)

Discussion/Conclusion

We are the first study that extensively investigated the association between the number of types of medications and HRQoL in dialysis patients. At 3 months after dialysis initiation, patients were prescribed on average 12 medications and almost all met the criteria for polypharmacy. We found an inverse linear association between the number of medications and PCS score and self-rated health. In addition, patients with 14–27 medications reported worse MCS scores and EQ-5D-5L utility scores and a higher number of symptoms and total symptom burden than pa-

tients with 2–10 medications. We found no significant differences in MCS score, number of symptoms, total symptom burden, and EQ-5D-5L utility score between patients with 11–13 and 2–10 medications. This suggests that medication regimens are well tolerated up to a certain threshold. If this threshold is exceeded, the number of medications can start to affect HRQoL negatively. Assuming a clinically important difference of 3 points in SF-12 summary scores, a clinically relevant difference is observed in PCS score for patients whose number of medications differs by 5 or more medications and in MCS score between patients with 14–27 and 2–10 medications.

The impact of medication on HRQoL can be conceived of as an equilibrium between the therapeutic benefits and the burden of medication. This burden can be broadly divided into 4 domains based on the domains presented by Mohammed et al. [34]. First, adhering to medication regimens is an arduous task for patients that becomes increasingly demanding with more medication [11]: a higher number of medications require more procedures to administer all medication, augment the number of drug intake moments, complicate keeping track when to take which medication, and may disrupt patients' daily lives, especially when medication must be taken during the day [34, 35]. Second, medication, and particularly polypharmacy, frequently causes additional symptoms through adverse events. These symptoms can restrict patients in their daily activities, cause mental distress, or lead to emergency room visits or hospitalization [13, 34, 36, 37]. Third, patients can find the number of medications itself and medication characteristics like taste, size, and route of administration burdensome [34, 38]. Finally, patients can consider the interaction with their physicians regarding their medication burdensome. Patients frequently have difficulties comprehending information about their medication and can feel reproached if physicians point out that they are taking their medication incorrectly [34].

An additional problem of polypharmacy is that non-adherence among patients is high, especially for patients who are more negligent in their self-care [35, 39]. This not only increases the likelihood of complications, which in itself reduce HRQoL, but also amplifies the number of medications required to treat complications, thereby possibly further reducing HRQoL.

Their large number of medications makes dialysis patients particularly prone to the above-mentioned factors, resulting in a sizeable medication burden. However, patients may not be aware of the therapeutic benefits of their medication since much of their medication is primarily prescribed to prevent the development or progression of

complications of kidney disease rather than alleviate symptoms [11, 40]. Hence, patients may, overall, predominantly be aware of the burden of medication.

A class of medication, which most notably may contribute to this burden, are phosphate binders since they taste unpleasant and are hard to swallow due to their size, and patients usually have to take multiple tablets up to 3 times a day, thereby significantly increasing the number of intake moments and pill burden [41, 42]. Interestingly enough, it appears as if dialysis modality does not affect the medication burden as haemodialysis and peritoneal dialysis patients are equally distributed across the medication tertiles. We did not distinguish between high-flux and low-flux haemodialysis nor online-haemodiafiltration and haemodialysis because they are not associated with benefits on various domains on quality of life compared to conventional haemodialysis [43, 44].

Previous studies among dialysis patients also report that polypharmacy is associated with lower quality of life. A US study in 233 haemodialysis patients reports a correlation between a higher number of medications and pill burden and lower PCS but not MCS scores. However, they did not report any effect estimates nor adjusted their results for possible confounders and only included oral and parenteral medications [16]. A Palestinian study in 267 haemodialysis patients reports that using 4 or more chronic medications was associated with worse EQ-5D-5L utility scores and self-rated health [17] and a Brazilian study in 200 haemodialysis patients found that using more medication was associated with worse outcomes for the physical functioning and mental health domains of the SF-36 [18]. Neither the Palestinian nor the Brazilian study describes which medication was included or gives detailed information on the number of medications their participants use: the former dichotomizes medication use in more or less than 4 medications, while the latter does not provide any information on medication use at all. The Brazilian study also did not report SF-36 summary scores. This makes comparing our results with these 2 studies challenging.

Our study has several strengths. First, we measured HRQoL in various ways, using multiple validated questionnaires with different measurement properties. Second, results were adjusted for several potential confounders, including comorbidity. At first sight, comorbidity may have biased our results due to confounding by indication. Since the prescription of medication and comorbidity are strongly correlated, the number of medications could be considered a proxy for the amount of comorbidity. In that case, not more medication but more comorbidity would explain lower HRQoL. Nevertheless, after ad-

justing for comorbidity with the CCI, observed HRQoL scores remained lower for patients using more medication, suggesting that medication itself, despite the possible role of comorbidity, also affects HRQoL. Third, to the best of our knowledge, this is the first study to examine the association between polypharmacy and HRQoL, which included both patients on haemodialysis and peritoneal dialysis. Fourth, we included both prescribed-as-needed and non-systemic medication in the number of medications. Fifth, multiple imputation reduced selection bias by limiting the number of excluded patients. Last, our results remained robust in sensitivity analyses, indicating that multiple imputation and using 6-month questionnaires did not introduce a significant information bias.

The main limitation of this study is that the cross-sectional design prevents us from demonstrating any causal relationship between polypharmacy and HRQoL. Other limitations are possible selection bias as we only used a subset of DOMESTICO patients or residual bias in observed associations, for example, through comorbidity that is unaccounted for in the CCI. Furthermore, we did not study several medication-related factors that also could affect HRQoL such as drug types, self-medication, and pill burden patients' attitudes toward medication. Especially pill burden may be an important medication-related determinant of HRQoL for dialysis patients as this is usually much higher than the number of medications [16].

In conclusion, this study provides evidence that a higher number of types of medications are associated with worse HRQoL in dialysis patients. This suggests that it is relevant to weigh expected therapeutic benefits of medication against their possible harmful effects on HRQoL. An unfavourable balance between expected benefits and an impact on HRQoL may be ground to be more liberal with adhering to clinical guidelines, especially for patients with a limited life expectancy or for whom a kidney transplant is unattainable. Further research should focus on corroborating our results in a longitudinal design and disentangling how and which medications and medication-related factors affect HRQoL. Most importantly, interventions should be developed for this vulnerable population that aim to reduce the medication burden, without disregarding long-term outcomes.

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Statement of Ethics

This study was approved by the Medical Research Ethics Committee of the Amsterdam UMC, Location VU Medical Centre (NL63277.029.17), and performed in accordance with the Declaration of Helsinki. All patients provided written informed consent before they were enrolled in the study.

Conflict of Interest Statement

A.A.B., A.E.S., A.C.A., and B.C.J. are involved in the DOMESTICO study (Netherlands Trial Register identifier: NL6519). All other authors have no conflicts of interest to declare.

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Author Contributions

A.A.B., A.E.S., A.C.A., and B.C.J. designed, secured funding, and set up the DOMESTICO study; J.M.T.C., A.A.B., and B.J. designed this study; A.A.B., A.E.S., J.A.B., A.O. A.H.B., A.C.A., and B.C.J. recruited patients; J.M.T.C. collected and analysed the data; J.M.T.C., A.A.B., A.C.A., and B.C.J. interpreted the results; and J.M.T.C. drafted the manuscript and made tables and figures. All authors provided intellectual content and critically edited, revised, and approved the manuscript.

Data Availability Statement

The data underlying this article are subject to an embargo of 12 months after completion of the DOMESTICO study. Once the embargo expires the data will be available upon reasonable request.

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