The value of dialysis and conservative care for older patients with advanced chronic kidney disease

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Health-related quality of life and symptoms of conservative care versus dialysis in patients with end-stage kidney disease: a systematic review

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ABSTRACT

Background

Non-dialytic conservative care has been proposed as a viable alternative to maintenance dialysis for selected older patients to treat end-stage kidney disease (ESKD). This systematic review compares both treatment pathways on health-related quality of life (HRQoL) and symptoms, which are major outcomes to patients and clinicians when deciding on preferred treatment.

Methods

We searched PubMed, Embase, Cochrane Library, CINAHL Plus, and PsycINFO from inception to October 1, 2019 for studies comparing patient-reported HRQoL outcomes or symptoms between patients who chose either conservative care or dialysis for ESKD.

Results

Eleven observational cohort studies were identified comprising 1718 patients overall. There were no randomized controlled trials. Studies were susceptible to selection bias and confounding. In most studies, patients who chose conservative care were older, had more comorbidities and worse functional status than patients who chose dialysis. Results were broadly consistent across studies, despite considerable clinical and methodological heterogeneity. Patient-reported physical health outcomes and symptoms appeared to be worse in patients who chose conservative care compared with patients who chose dialysis but were not started yet, but similar compared with patients on dialysis. Mental health outcomes were similar between patients who chose conservative care or dialysis, including before and after dialysis start. In patients who chose dialysis, the burden of kidney disease and impact on daily life increased after dialysis start.

Conclusions

The available data, while heterogeneous, suggest that in selected older patients conservative care has potential to achieve similar HRQoL and symptoms compared with a dialysis pathway. High-quality prospective studies are needed to confirm these provisional findings.

INTRODUCTION

The number of patients with end-stage kidney disease (ESKD) is increasing worldwide [1, 2]. The fastest growing group is represented by older patients. Among older patients, dialysis has become the most common treatment for ESKD [3]. Nowadays, the majority of all patients on maintenance dialysis is aged >65 years old in many countries [4, 5]. Older patients are more often frail, have multiple chronic conditions and more functional impairment than younger patients [6]. Since dialysis is an intensive treatment, its suitability in older patients has been questioned [7]. Non-dialytic conservative care has been proposed as alternative to dialysis for selected older patients with ESKD [8-10]. With the intention to be provided until death, conservative care aims to preserve quality of life with adequate symptom control by active medical treatment and multidisciplinary care including all interventions needed, except dialysis [8].

Data on patient-relevant outcomes are needed to evaluate whether conservative care is a viable alternative to dialysis and, if so, to help inform the shared decision-making process between patients and healthcare professionals on possible treatment for ESKD [11, 12]. Most studies, however, assessed survival only. These observational studies showed that in selected patients the survival benefit of a dialysis pathway was limited or absent compared with conservative care, particularly in the oldest patients and patients with multiple comorbidities [13, 14]. Patients consider other outcomes than survival to be important as well when deciding on conservative care or dialysis, including health-related quality of life (HRQoL) and symptoms [15-19]. The need for more patient-relevant data on both treatment pathways has recently been recognized as research priority by patients, clinicians, and organizations like Kidney Disease: Improving Global Outcomes (KDIGO) [8, 20-23]. Six systematic reviews have been performed to summarize evidence on HRQoL and symptoms in patients who chose either conservative care or a dialysis pathway [24-29], but studies included limited search strategies [24-29] or have become outdated [24, 28, 29]. An updated and more comprehensive overview of current evidence on HRQoL and symptoms in both treatment pathways is needed.

The aim of this systematic review was to compare patient-reported outcomes on HRQoL and symptoms between patients who chose either conservative care or a dialysis pathway for ESKD. We aimed to include studies that evaluated outcomes from the moment

of treatment decision or subsequent time points, since an equivalent time point for treatment start itself is difficult to identify in both treatment pathways [30].

MATERIALS AND METHODS

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31]. Methods of the analysis and selection criteria were documented in advance in a protocol published on PROSPERO [32].

Search strategy

We identified studies by searching PubMed, Embase, Cochrane Library, CINAHL Plus, and PsycINFO from inception to October 1, 2019. A proposal for search terms was pilot tested and reviewed by an external clinical librarian. The final search strategy included terms relating to or describing the intervention (conservative care), the comparative intervention (dialysis pathway), and the patient population (advanced chronic kidney disease or ESKD). Supplementary Table S1 shows full search terms. We searched for additional studies by checking the reference lists and citations of included studies via Scopus and by expert consultation.

Study selection

Two authors (W.R.V., I.D.W.) independently screened the titles and abstracts of all search hits for eligibility. Full texts of potentially relevant studies were retrieved and independently assessed for final eligibility. Pre-defined criteria on inclusion and exclusion were used (Supplementary Table S1). We selected original research articles if they included a comparison of patient-reported outcomes on HRQoL or symptoms between patients who chose either conservative care or a dialysis pathway. In all patients, an explicit decision in favour of conservative care or dialysis had to been made, without further selecting on how or by whom the treatment decision was made. We defined conservative care as non-dialytic care for ESKD intended to be provided until death (not just to postpone dialysis) [8]. Patients on a dialysis pathway included both patients who chose dialysis but were not started yet and patients who started or were already receiving dialysis. Studies in patients with acute kidney injury and non-English publications were excluded. Disagreements were resolved through consensus discussion, consultation of a third author (W.J.W.B.), and contact with authors of original studies for additional information.

Data extraction

Data from included studies were independently extracted by two authors (W.R.V., I.D.W.) using a standardized, pre-piloted form. The extracted data included information on: study setting; study population; participant characteristics; study methodology; measurement tools and study results of HRQoL and symptoms; and information to assess risk of bias. Discrepancies in data extraction were resolved through consensus discussion.

Study quality assessment

Two authors (W.R.V., I.D.W.) independently appraised risk of bias of included studies using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) [33, 34]. This tool assesses six domains of bias with criteria to determine a low risk, high risk, or unclear risk of bias (selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting). Disagreements in assessed risk of bias were resolved through consensus discussion and consultation of a third author (W.J.W.B.).

Data synthesis

The findings of included studies were synthesized qualitatively. We subdivided results of patients on a dialysis pathway according to dialysis start and modality, and in patients on conservative care according to an estimated glomerular filtration rate (eGFR) <10 mL/min/1.73 m^2 as surrogate time point for dialysis start. We planned to perform a meta-analysis in case of sufficiently homogeneous data [32]. After careful consideration, however, performing a meta-analysis was deemed inappropriate due to wide variability in study design, study population, exposure, analysis and reporting of study outcomes.

RESULTS

Search results

We screened 4059 unique search hits identified through database searching, leaving 338 articles for full-text assessment (Figure 1). We excluded 327 full-text articles because studies did not include the population or outcomes of interest or described no original research. We contacted the authors of four studies to clarify the definition of their conservative care-like patient group. All authors responded and answered that their patient group did not correspond with our definition of conservative care, making these studies not eligible for inclusion (Supplementary Table S2). Our search resulted in eleven relevant studies

comparing HRQoL outcomes or symptoms between patients who chose either conservative care or a dialysis pathway [35-45]. No randomized controlled trials were identified.

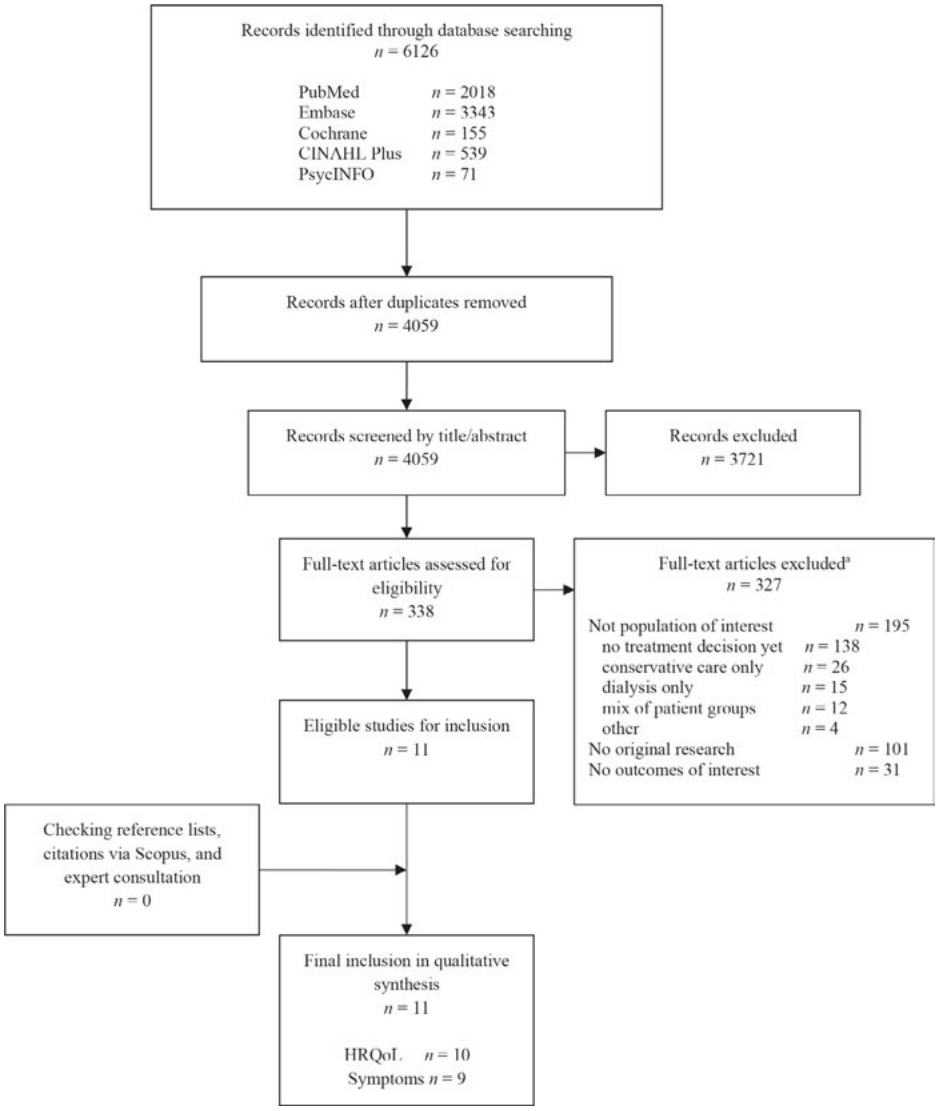

Figure 1. Study inclusion and exclusion flow diagram.
[a] Explanation of reasons for exclusion: No treatment decision yet includes patients with advanced chronic kidney disease who did not, or did not yet have to, decide on preferred treatment (commonly referred to as "non-dialysis dependent chronic kidney disease patients"), including 4 studies discussed with the authors to clarify their conservative care-like patient group (Supplementary Table S2); Mix of patient groups means mix of different patient categories into one patient group without subgroup analyses (*e.g.*, mix of patients who have not made a treatment decision yet and patients who chose conservative care); No original research, for example reviews, opinion papers, or study protocols.

Study characteristics

Table 1 summarizes characteristics of the studies included. Studies were published between 2009 and 2019 and originated from Europe, Asia, and Australia. Studies were observational cohort studies performed in a single center (n = 8) or multiple centers (n = 3). Sample size varied from 11 to 395 patients per study (1718 patients overall: 1069 on a dialysis pathway, 649 on conservative care). Seven studies included only older patients using a threshold in the range of ≥60 to ≥75 years old [38-44]. The patient group on a dialysis pathway varied per study: some included patients in whom a decision in favour of dialysis had been made but who were not started on dialysis yet [35, 39]; other studies mixed such patients with patients who started dialysis [36-38]; while most studies included patients receiving dialysis (hemodialysis, peritoneal dialysis, or assisted peritoneal dialysis) [39-45]. Studies also used different inclusion criteria on severity of advanced chronic kidney disease, among which two studies focused on patients with an eGFR <10 mL/min/1.73 m^2 [41, 42]. The reported approach to conservative care was generally similar among the studies. Six studies assessed outcomes at a single time point [36, 39-42, 45], while five studies performed multiple measurements over time including a baseline measurement [35, 37, 38, 43, 44]. Time points of outcome measurements ranged from three months after treatment decision or dialysis start to 36 months after decision or recruitment or 139 months after dialysis start.

Risk of bias

Figure 2 shows that seven studies had a high risk of selection bias, particularly one study since they non-randomly selected patients on hemodialysis as a rough reference [40]. Six studies had a high risk of confounding as no adjustment for any confounder was reported [35, 36, 40, 43-45]. Risk of bias due to incomplete outcome data was high in two studies because of low response rates (49-56% [35]; 30-56% [36]). Other risk of bias domains were assessed low, or unclear due to missing information. Supplementary Table S3 shows the risk of bias assessment per study.

Table 1. Characteristics of studies included in the systematic review

Study	Country	Design[a]	N	Inclusion criteria	Dialysis patient group	Reported conservative care strategy	Patient-reported outcome measure		Time points of outcome measurement
							HRQoL	*Symptoms*	
Brown 2015 [35]	Australia	Cohort	395	CKD stage 4/5 No age criterion	Choice D	Usual nephrology care and renal supportive care clinic	SF-36	MSAS-SF	At baseline + 12 months after first visit to predialysis or renal supportive care clinic
Yuen 2016 [36]	Hong Kong	Cohort	268	CKD stage 4/5 Adults	Mix of choice D and on D (27%, modality unknown)	Renal palliative care clinic	SF-36	n/a	Not reported
Da Silva-Gane 2012 [37]	United Kingdom	Cohort	154	CKD stage 4/5 No age criterion	Choice HD, 59% started during follow-up Choice PD, 52% started	Active medical treatment and multidisciplinary care	SF-36 SWLS	HADS (anxiety + depressive symptoms)	Every 3 months for up to 36 months after recruitment; until 12 months after dialysis start
Seow 2013 [38]	Singapore	Cohort	101	eGFR 8-12 ≥75 years or age-adjusted CCI ≥8	Choice D, 100% started during follow-up (modality unknown)	Not reported	KDQOL-SF	KDQOL-SF	Multiple measurements during 24 months after recruitment
Verberne 2018 [39]	Netherlands	Cohort	96	CKD stage 4/5 ≥70 years	Choice D On D (76% HD, 24% PD)	Active medical treatment and multidisciplinary care	KDQOL-SF	KDQOL-SF	At median 13 (choice D), 35 (on D), and 16 months (CC) after treatment decision
De Biase 2008 [40]	Italy	Cohort	11	eGFR <15 >75 years	On HD	Usual nephrology care and round-the-clock telephone support service	SF-36	STAI-Y BDI	At median 17 (dialysis) and 13 months (CC); not reported from which starting point
Iyasere 2018 [41]	United Kingdom	Cohort Multicenter (n = 21)	84	eGFR <10 ≥60 years >6 months life expectancy	On HD On aPD	Active non-dialysis care	SF-12 IIRS	POS-S renal HADS (depressive symptoms)	Majority at 13-60 months after dialysis start; not reported for CC group

Table 1. *(continued)*

Study	Country	Design[a]	N	Inclusion criteria	Dialysis patient group	Reported conservative care strategy	Patient-reported outcome measure		Time points of outcome measurement
							HRQoL	*Symptoms*	
Shah 2019 [42]	United Kingdom, Australia	Cohort Multicenter (n = 3)	129	eGFR <10 ≥75 years	On D (84% HD, 16% PD)	Comprehensive conservative, non-dialytic care	KDQOL-36	KDQOL-36	Not reported (cross-sectional)
Tan 2017 [43]	Australia	Cohort	20	eGFR <15 >65 years	On D (42% HD, 58% PD)	Renal supportive care clinic	n/a	POS-S renal	At baseline + 6 months after dialysis start or first visit to renal supportive care clinic
Van Loon 2019 [44]	Netherlands	Cohort Multicenter (n = 17)	281	eGFR<15 ≥65 years	On D (77% HD, 23% PD)	Maximal conservative management	EQ-5D-3L	n/a	At baseline + 6 months after dialysis start or treatment decision (CC)
Yong 2009 [45]	Hong Kong	Cohort	179	eGFR <15 Adults	On D (20% HD, 80% PD)	Renal palliative care clinic	SF-36	Self-created symptom list BPI	At mean 139 (HD) or 49 (PD) months after dialysis start, and 11 months after treatment decision (CC)

[a] Study setting is single center or indicated if otherwise.

aPD, assisted peritoneal dialysis; BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; CC, conservative care; CCI, Charlson Comorbidity Index; choice D, patients who had chosen but not yet started dialysis; CKD, chronic kidney disease; D, dialysis (including all dialysis modalities); eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); EQ-5D-3L, EuroQOL-5D-3L; HADS, Hospital Anxiety and Depression Scale (used version is indicated); HD, hemodialysis; HRQoL, health-related quality of life; IIRS, Illness intrusiveness rating scale; KDQOL-SF, Kidney Disease Quality of Life-Short Form (79 items, including the SF-36 and eight kidney disease-specific domains); KDQOL-36, Kidney Disease Quality of Life-Short Form (36 items, including the SF-12 and three kidney disease-specific domains); MSAS-SF, Memorial Symptom Assessment Scale; N, overall sample size; n/a, not applicable; PD, peritoneal dialysis; POS-S renal, Palliative care Outcome Scale – Symptoms (Renal); SF-12, Short Form-12; SF-36, Short Form-36; STAI-Y, State Trait Anxiety Inventory; SWLS, Satisfaction with Life Scale.

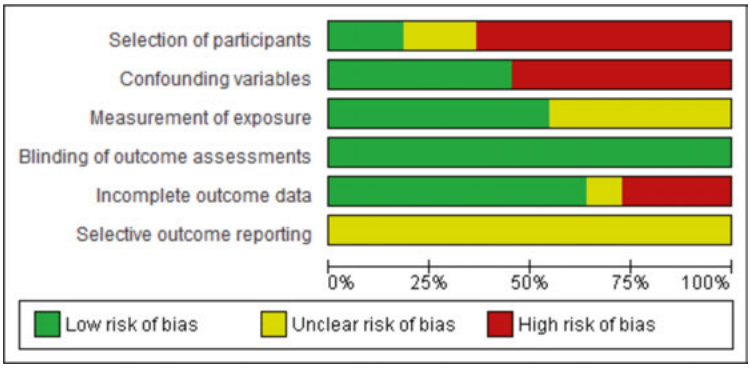

Figure 2. Overall risk of bias, using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) [33]. Supplementary Table S3 shows the risk of bias assessment per study.

Patient characteristics

Table 2 shows characteristics of the patient groups who chose either conservative care or dialysis. Patients on conservative care were older (mean age ranging from 73 to 84 years old) than patients on a dialysis pathway (48 to 83 years old) and were more often female. An exception is one study that included patients by propensity-matching on age and sex [41]. The comorbidity level was higher in patients on conservative care compared with patients on a dialysis pathway in six studies [35-37, 40, 43, 45], while similar in four studies [38, 39, 41, 44]. Seven studies reported functional status and observed functional impairment in both patient groups, which was often worse in patients on conservative care than in patients on a dialysis pathway.

Health-related quality of life

Ten studies reported HRQoL outcomes. Table 3 shows the results per HRQoL domain. Supplementary Table S4 shows the results per study including baseline values where applicable.

Table 2. Patient characteristics of the dialysis and conservative care patient groups per included study

Study	Number of patients		Mean age		Female (%)		Mean eGFR at baseline		High comorbidity		Impaired functional status or frailty	
	D	*CC*	*D*	*CC*	*D*	*CC*	*D*	*CC*	*D*	*CC*	*D*	*CC*
Brown, 2015 [35]	273 choice D	122	67	82	33	45	16	16	18% ≥3 comorbidities[c]	38% ≥3 comorbidities[c]	NR	NR
Yuen, 2016 [36]	79 mix D[a]	189	59	77	NR	NR	11	13	Mean mCCI 6.2	Mean mCCI 8.9	13% impaired mobility	53% impaired mobility
Da Silva-Gane, 2012 [37]	80 choice HD 44 choice PD	30	61 48	78	24 50	30	13 14	14	35% high comorbidity[d] 14% high comorbidity[d]	74% high comorbidity[d]	18% KPS <70 2% KPS <70	66% KPS <70
Seow, 2013 [38]	38 choice D	63	71	78	47	44	10	10	Median CCI 5	Median CCI 5	Median KPS 60	Median KPS 60
Verberne, 2018 [39]	39 choice D 34 on D	23	80 80	84	31 25	46	16 n/a	16	28% high comorbidity[e] 32% high comorbidity[e]	26% high comorbidity[e]	NR	NR
De Biase, 2008 [40]	5 on HD	6	79	82	NR	36	n/a	8	Median number 2[f]	Median number 6[f]	Mean KPS 70	Mean KPS 84
Iyasere, 2018 [41]	28 on HD[b] 28 on aPD[b]	28[b]	82[b] 81[b]	83[b]	57[b] 50[b]	50[b]	n/a	NR	Median Davies score 2[b] Median Davies score 2[b]	Median Davies score 1[b]	Median frailty score 4[h] Median frailty score 5[h]	Median frailty score 4[h]
Shah, 2019 [42]	83 on D	46	83	81	33	41	n/a	NR	NR	NR	NR	NR
Tan, 2017 [43]	12 on D	8	73	84	25	50	n/a	11	8% CCI >5	50% CCI >5	51% KPS <70	50% KPS <70
Van Loon, 2019 [44]	192 on D	89	82	75	31	44	8	12	41% high comorbidity[g]	44% high comorbidity[g]	77% frail[i]	88% frail[i]
Yong, 2009 [45]	134 on D	45	58	73	48	54	n/a	NR	Mean mCCI 6.1	Mean mCCI 8.5	NR	NR

[a] 27% were being treated with dialysis (dialysis modality unknown), the rest had not started dialysis yet.
[b] CC patients were propensity-matched to HD and aPD patients by age, gender, ethnicity, diabetes status and index of deprivation.
[c] Comorbidities included ischemic heart disease or cardiac failure, cerebrovascular or peripheral vascular disease, chronic liver or lung disease, diabetes, and dementia.
[d] Comorbidity score included cardiac disease, peripheral vascular disease, central nervous disease, and respiratory disease. Severity ranged from 0 (no disease) to 4 (advanced disease). Cancer was graded similarly, cirrhosis was scored as 4. Patients with summed scores >3, or score of 3 derived from a single system, were considered to have high comorbidity.
[e] The Davies comorbidity score was used, in which a score ≥3 is defined as high comorbidity.
[f] Comorbidities included dementia, diabetes mellitus, hypoacusia, heart failure, hypertension, ischemic heart disease, osteoarthritis, stroke, arrhythmia, urinary incontinence, chronic obstructive lung disease, bedsores, neoplasms and hypothyroidism.
[g] The Cumulative Illness Rating Scale-Geriatrics was used, in which ≥2x score 3 or ≥1x score 4 was considered high comorbidity.
[h] Clinical Frailty Scale (higher scores represent increasing levels of frailty).

Table 2. *(continued)*
[i] Frailty was measured with a geriatric assessment. Impairments in ≥2 geriatric domains was considered as frail. aPD, assisted peritoneal dialysis; *CC*, conservative care patient group; CCI, Charlson Comorbidity Index (higher score represents higher comorbidity burden); mCCI, modified Charlson Comorbidity Index (higher score represents higher comorbidity burden); choice D, patients who had chosen but not yet started dialysis; *D*, dialysis patient group; D, dialysis (modalities unspecified); eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); HD, hemodialysis; KPS, Karnofsky performance scale (lower score represents worse functional status); mix D, mix of patients who had selected dialysis but not yet started dialysis and patients who were being treated with dialysis; n/a, not applicable; NR, not reported; on D, patients being treated with dialysis; PD, peritoneal dialysis.

Nine studies assessed physical and mental health domains using the Short Form-36 (SF-36) or Short Form-12 (SF-12) [35-42, 45]. Lower physical health outcomes were observed in patients who chose conservative care compared with patients who chose dialysis but were not started yet, including the physical component summary, physical function, and general health domains [35-37, 39]. Similar physical health outcomes were observed between patients who chose conservative care and patients on dialysis, including patients with an eGFR <10 ml/min/1.73 m^2 and different dialysis modalities [37-42, 45]. In repeated measurements over 12 to 36 months, physical health outcomes showed similar trajectories in both patient groups [35, 37, 38], including after dialysis start in patients who chose dialysis [37, 38].

Mental health outcomes, including the mental component summary vitality, social function, role emotional, and mental health domains, were similar between patients who chose either conservative care or a dialysis pathway, including patients with an eGFR <10 ml/min/1.73 m^2, before and after dialysis start and per dialysis modality [35-42, 45]. When measured repeatedly over 12 to 36 months, mental health outcomes showed similar trajectories in both patient groups [35, 37, 38], including after dialysis start in patients who chose dialysis [37, 38].

Three studies examined kidney disease-specific HRQoL domains [38, 39, 42]. Patients who chose conservative care scored similar [39], or better than patients on dialysis on effects of kidney disease on daily life [38, 42]. Furthermore, patients who chose conservative care scored better on burden of kidney disease compared with patients on dialysis [38, 39, 42]. In patients on a dialysis pathway, both domain scores decreased after dialysis start [38]. In another study, scores on life satisfaction also decreased after dialysis start [37]. Illness intrusiveness scores were similar between patients on either conservative care or dialysis [41]. One study observed a small decline in general health status of the EuroQOL-5D after treatment decision in patients who chose conservative care, while patients who started dialysis scored similar after six months [44].

Table 3. Study results per outcome domain of health-related quality of life

Outcome	Study	Effect estimate	Results dialysis patient group			Results conservative care		Statistical significance	Adjusted
SF-36, SF-12			*Before start*	*After start*	*Combined*	*Combined eGFR><10*	*eGFR <10 mL/ min/1.73 m²*		
Physical Component Summary	Brown, 2015 [35]	% worse/stable/improved	55/4/41			63/16/21		$P = 0.12$	No
	Da Silva-Gane, 2012 [37]	Change per month (mean)			+0.04	+0.04		± 0.17, "non-significant"	Yes[a]
		Change after dialysis start (mean)		+0.49				± 1.7, $P = 0.53$	Yes[a]
	Seow, 2013 [38]	B coefficient per month	-0.29	-0.30		-0.10		$P = 0.07$	Yes[b]
		B coefficient after dialysis start		+1.72				-0.57 to 4.01, $P = 0.14$	Yes[b]
	Verberne, 2018[f] [39, 72]	Mean	38.3			30.9		$P < 0.01$	No
		B coefficient	+6.61			ref.		1.79 to 11.43, $P < 0.01$	Yes[c]
		Mean		34.2		30.9		$P = 0.38$	No
		B coefficient		+2.20		ref.		–2.79 to 7.20, $P = 0.38$	Yes[c]
	Iyasere, 2018 [41]	Median		29.2 (HD)			28.9	$P = 0.62$	No
		Median		30.8 (aPD)					
		Beta coefficient		1.08 (HD)			ref.	0.89 to 1.29, $P = 0.45$	Yes[d]
		Beta coefficient		1.20 (aPD)			ref.	1.00 to 1.45, $P = 0.05$	Yes[d]
	Shah, 2019 [42]	Mean		31.2			34.3	"Non-significant"	No
		B coefficient		-3.17			ref.	-7.61 to 1.27, $P = 0.16$	Yes[e]
Mental Component Summary	Brown, 2015 [35]	% worse/stable/improved	45/2/53			42/5/53		$P = 0.78$	No
	Da Silva-Gane, 2012 [37]	Change per month (mean)			+0.12	+0.12		± 0.32, $P < 0.05$	Yes[a]
		Change after dialysis start (mean)		-0.68				± 5.84, $P = 0.53$	Yes[a]
	Seow, 2013 [38]	B coefficient per month	+0.01	-0.09		+0.13		$P = 0.89$	Yes[b]
		B coefficient after dialysis start		-0.26				-3.39 to 2.86, $P = 0.87$	Yes[b]
	Verberne, 2018[f] [39, 72]	Mean	52.8			47.5		$P = 0.17$	No
		B coefficient	+6.45			ref.		1.48 to 11.41, $P = 0.01$	Yes[c]
		Mean		50.5		47.5		$P = 0.58$	No
		B coefficient		-0.58		ref		–5.80 to 4.64, $P = 0.83$	Yes[c]

Table 3. *(continued)*

Outcome	Study	Effect estimate	Results dialysis patient group			Results conservative care		Statistical significance	Adjusted
SF-36, SF-12			*Before start*	*After start*	*Combined*	*Combined eGFR><10*	*eGFR <10 mL/ min/1.73 m²*		
	Iyasere, 2018 [41]	Median		49.9 (HD)			46.3	$P = 0.68$	No
		Median		50.2 (aPD)					
		Beta coefficient		1.03 (HD)			ref.	0.87 to 1.22, $P = 0.71$	Yes[d]
		Beta coefficient		1.07 (aPD)			ref.	0.90 to 1.27, $P = 0.44$	Yes[d]
	Shah, 2019 [42]	Mean		47.7			46.6	"Non-significant"	No
		B coefficient		-2.41			ref.	-7.66 to 2.84, $P = 0.37$	Yes[e]
Physical function	Yuen, 2016 [36]	Mean			88.7	81.2		$P < 0.001$	No
	Verberne, 2018 [39]	Median	50.0			25.0		$P < 0.001$	No
		Median		30.0		25.0		$P = 0.25$	No
	De Biase, 2008 [40]	Mean		45		28		Not reported	No
	Yong, 2009 [45]	Mean		55.9		43.8		Not reported	No
Role physical	Yuen, 2016 [36]	Mean			81.8	75.5		$P = 0.77$	No
	Verberne, 2018 [39]	Median	50.0			25.0		$P = 0.63$	No
		Median		25.0		25.0		$P = 0.83$	No
	De Biase, 2008 [40]	Mean		15		25		Not reported	No
	Yong, 2009 [45]	Mean		42.5		53.3		Not reported	No
Bodily pain	Yuen, 2016 [36]	Mean			83.5	78.9		$P = 0.12$	No
	Verberne, 2018 [39]	Median	80.0			57.5		$P = 0.10$	No
		Median		73.8		57.5		$P = 0.06$	No
	De Biase, 2008 [40]	Mean		62		47		Not reported	No
	Yong, 2009 [45]	Mean		75.2		72.8		Not reported	No
General health	Yuen, 2016 [36]	Mean			53.9	50.3		$P < 0.001$	No
	Verberne, 2018 [39]	Median	50.0			35.0		$P < 0.005$	No
		Median		37.5		35.0		$P = 0.57$	No
	De Biase, 2008 [40]	Mean		46		41		Not reported	No
	Yong, 2009 [45]	Mean		38.2		42.4		Not reported	No
Vitality	Yuen, 2016 [36]	Mean			61.5	60.4		$P = 0.94$	No
	Verberne, 2018 [39]	Median	60.0			45.0		$P < 0.005$	No
		Median		57.5		45.0		$P = 0.03$	No
	De Biase, 2008 [40]	Mean		51		47		Not reported	No
	Yong, 2009 [45]	Mean		51.2		49.0		Not reported	No

Table 3. *(continued)*

Outcome	Study	Effect estimate	Results dialysis patient group			Results conservative care		Statistical significance	Adjusted
SF-36, SF-12			*Before start*	*After start*	*Combined*	*Combined eGFR>=10*	*eGFR <10 mL/ min/1.73 m²*		
Social function	Yuen, 2016 [36]	Mean			92.9	92.2		$P = 0.49$	No
	Verberne, 2018 [39]	Median	87.5			62.5		$P = 0.01$	No
		Median		62.5		62.5		$P = 0.69$	No
	De Biase, 2008 [40]	Mean		75		77		Not reported	No
	Yong, 2009 [45]	Mean		65.8		73.6		Not reported	No
Role emotional	Yuen, 2016 [36]	Mean			77.7	77.9		$P = 0.37$	No
	Verberne, 2018 [39]	Median	100.0			100.0		$P = 0.81$	No
		Median		100.0		100.0		$P = 0.79$	No
	De Biase, 2008 [40]	Mean		60		40		Not reported	No
	Yong, 2009 [45]	Mean		50.5		68.9		Not reported	No
Mental health	Yuen, 2016 [36]	Mean			74.5	75.7		$P = 0.008$	No
	Verberne, 2018 [39]	Median	84.0			76.0		$P = 0.001$	No
		Median		84.0		76.0		$P = 0.03$	No
	De Biase, 2008 [40]	Mean		67		67		Not reported	No
	Yong, 2009 [45]	Mean		67.1		73.5		Not reported	No
KDQOL-SF or KDQOL-36									
Effects of kidney disease on daily life	Seow, 2013 [38]	B coefficient per month	-0.34	-0.25		+0.30		$P = 0.01$	Yes[b]
		B coefficient after dialysis start		-3.86				-0.74 to -0.31, $P = 0.03$	Yes[b]
	Verberne, 2018 [39]	Median	92.9			82.7		$P = 0.03$	No
		Median		85.7		82.7		$P = 0.35$	No
	Shah, 2019 [42]	Mean		64.2			81.3	$P < 0.001$	No
		B coefficient		-16.49			ref.	-25.98 to -6.99, $P < 0.001$	Yes[e]
Burden of kidney disease	Seow, 2013 [38]	B coefficient per month	-0.58	-0.65		+0.54		$P < 0.00$	Yes[b]
		B coefficient after dialysis start		-25.11				-32.2 to -18.1, $P < 0.001$	Yes[b]
	Verberne, 2018 [39]	Median	75.0			75.0		$P = 0.70$	No
		Median		43.8		75.0		$P = 0.001$	No
	Shah, 2019 [42]	Mean		34.7			62.8	$P < 0.001$	No
		B coefficient		-28.59			ref.	-41.77 to -15.42, $P < 0.001$	Yes[e]

Table 3. *(continued)*

Outcome	Study	Effect estimate	Results dialysis patient group			Results conservative care		Statistical significance	Adjusted
			Before start	*After start*	*Combined*	*Combined eGFR><10*	*eGFR <10 mL/ min/1.73 m²*		
Other PROMs									
Illness intrusiveness rating scale	Iyasere, 2018 [41]	Median		31.0 (HD)			30.5	$P = 0.79$	No
		Median		32.0 (aPD)					
		Beta coefficient		1.17 (HD)			ref.	0.93 to 1.48, $P = 0.19$	Yes[d]
		Beta coefficient		1.11 (aPD)			ref.	0.86 to 1.42, $P = 0.42$	Yes[d]
Satisfaction with life scale	Da Silva-Gane, 2012 [37]	Change per month (mean)			+0.02	+0.02		± 0.11, "non-significant"	Yes[a]
		Change after dialysis start (mean)		-1.84				± 4.50, $P = 0.01$	Yes[a]
EQ-5D Index score	Van Loon, 2019 [44]	Change after 6 months (mean)		+0.026		-0.047		$P < 0.01$	No
EQ-5D self-rated health score	Van Loon, 2019 [44]	Change after 6 months (mean) (scale 0 – 10)		+0.3		-0.4		$P < 0.01$	No

[a] Mean changes were adjusted for age, sex, comorbidity score, Karnofsky performance score, and propensity score (Da Silva-Gane, 2012 [37]).
[b] B coefficients were adjusted for age, comorbidity score, Karnofsky performance score, primary renal disease, and change in estimated glomerular filtration rate (Seow, 2013 [38]).
[c] B coefficients were adjusted for sex, and way of administration. Similar results when also adjusted for age, and comorbidity score (Verberne, 2018 [39, 72]).
[d] All analyses were performed in propensity-matched patients. Beta coefficients were adjusted for age, sex, comorbidity score, frailty, and dialysis vintage (Iyasere, 2018 [41]).
[e] B coefficients were adjusted for age, sex, country, education, and health insurance (Shah, 2019 [42]).
[f] Results on the PCS and MCS were included from a reanalysis in which the same scoring algorithm as in similar studies was used (Verberne, 2019 [39, 72]).
aPD, assisted peritoneal dialysis; eGFR, estimated glomerular filtration rate (mL/min/1.73 m²); EQ-5D, EuroQOL-5D-3L (score of 1 is perfect health in EQ-5D Index); HD, hemodialysis; IIRS, Illness intrusiveness rating scale (score range: 13-91, higher scores represent more illness intrusion); KDQOL-SF, Kidney Disease Quality of Life-Short Form (79 items, including the SF-36 and eight kidney disease-specific domains; score range: 0-100, higher scores represent better quality of life); KDQOL-36, Kidney Disease Quality of Life-Short Form (36 items, including the SF-12 and three kidney disease-specific domains; score range: 0-100, higher scores represent better quality of life); PD, peritoneal dialysis; PROMs, patient-reported outcome measures; ref., reference group; SF-12, Short Form-12 (score range: 0-100, higher scores represent better quality of life); SF-36, Short Form-36 (score range: 0-100, higher scores represent better quality of life); SWLS, Satisfaction with Life Scale (score range: 5-35, higher scores represent higher satisfaction with life).

Symptoms

Table 4 shows the results of the nine studies comparing symptoms by overall symptom scores (n = 7), or domain scores on depressive symptoms (n = 3), anxiety (n = 2), cognitive function (n = 2), sleep (n = 2), and pain (n = 1) [35, 37-43, 45]. Patients who chose conservative care reported a higher overall symptom burden than patients who chose dialysis but were not started yet [35, 39] and patients on assisted peritoneal dialysis [41], but similar compared with patients on hemodialysis or unassisted peritoneal dialysis [36, 39, 41-43]. When measured repeatedly over 12 to 24 months, two studies observed similar trajectories of symptom burden in both patients on conservative care or a dialysis pathway [35, 38], including after dialysis start in patients who chose dialysis [38]. One small study found less improvement of symptoms in patients on conservative care compared with patients started with dialysis after 6 months [43]. Patients who chose conservative care reported more dyspnea, drowsiness, and poor mobility than patients on dialysis, but less pruritus, skin changes, halitosis, sexual problems, bloated abdomen, and limb numbness [43, 45].

Two studies found more depressive symptoms in patients who chose conservative care compared with patients on hemodialysis [40, 41], while scores were stable over 36 months in both patient groups and did not change after dialysis start [37]. No differences between both patient groups were reported on anxiety [37, 40], cognitive function [38, 39], sleep [38, 39], and pain [45]. Patients who chose dialysis reported an improvement in cognitive function after dialysis start [38].

Table 4. Results on symptoms per study

Study	PROM	Outcome domain	Effect estimate	Results dialysis patient group			Results conservative care	Statistical significance	Adjusted for
				Before start	*After start*	*Combined*	*Combined eGFR <10 mL/ eGFR><10 min/1.73 m²*		
Brown, 2015 [35]	MSAS-SF	Symptom score	Mean at baseline	9.1			12.2	$P < 0.001$	Not adjusted
			% worse/stable/improved after 12 months	58/31/10			38/57/5	$P = 0.12$	
Da Silva-Gane, 2012 [37]	HADS	Anxiety	Mean at baseline	5.5 (HD)			6.9	$P = 0.04$	Age, sex, comorbidity score, KPS score, propensity score (mean changes)
			Mean at baseline	4.7 (PD)			6.9	$P = 0.02$	
			Change per month (mean)			-0.004	-0.004	± 0.14, "non-significant"	
			Change after dialysis start (mean)		-0.02			± 2.6, $P = 0.95$	
		Depressive symptoms	Mean at baseline	6.1 (HD)			5.2	"Non-significant"	
			Mean at baseline	6.4 (PD)			5.2	"Non-significant"	
			Change per month (mean)			-0.03	-0.03	± 0.10, "non-significant"	
			Change after dialysis start (mean)		-0.57			± 1.7, $P = 0.10$	
Seow, 2013 [38]	KDQOL-SF	Symptoms/ Problems	B coefficient per month	-0.21	-0.17		+0.002	$P = 0.10$	Age, comorbidity score, KPS score, primary renal disease, change in eGFR
			B coefficient after dialysis start		+2.63			-0.01 to 5.28, $P = 0.05$	
		Cognitive function	B coefficient per month	+0.30	-0.22		-0.09	$P = 0.001$	
			B coefficient after dialysis start		+7.58			3.50 to 11.65, $P < 0.001$	
		Sleep	B coefficient per month	-0.54	-0.15		+0.14	$P = 0.08$	
			B coefficient after dialysis start		+2.40			-2.06 to 6.86, $P = 0.29$	
Verberne, 2018 [39]	KDQOL-SF	Symptoms/ Problems	Median	86.4			72.6	$P = 0.03$	Not adjusted
			Median		83.3		72.6	$P = 0.05$	
		Cognitive function	Median	86.7			73.3	$P = 0.01$	
			Median		86.7		73.3	$P = 0.09$	
		Sleep	Median	70.0			65.0	$P = 0.19$	
			Median		66.3		65.0	$P = 0.66$	

Table 4. *(continued)*

Study	PROM	Outcome domain	Effect estimate	Results dialysis patient group			Results conservative care		Statistical significance	Adjusted for
				Before start	*After start*	*Combined*	*Combined eGFR><10*	*eGFR <10 mL/ min/1.73 m²*		
Shah, 2019 [42]	KDQOL-36	Symptoms/ Problems	Mean		70.7			76.6	"Non-significant"	Age, sex, country, education, health insurance (b coefficient)
			B coefficient		-5.93			ref.	-14.61 to 2.73, *P* = 0.18	
De Biase, 2008 [40]	STAI-Y	Anxiety	% with anxiety		0		0		Not reported	Not adjusted
	BDI	Depressive symptoms	% with depressive symptoms		20		50			
Iyasere, 2018 [41]	POS-S renal	Symptom score	Median		22 (HD)			20	*P* = 0.10	Age, sex, comorbidity score, frailty score, dialysis vintage (beta coefficients)
			Median		16 (aPD)					
			Beta coefficient		0.90 (HD)			ref.	0.66 to 1.21, *P* = 0.48	
			Beta coefficient		0.62 (aPD)			ref.	0.43 to 0.90, *P* = 0.01	
	HADS	Depressive symptoms	Median		5 (HD)			7	*P* = 0.03	
			Median		7.5 (aPD)					
			% score >7		25 (HD)			46	*P* = 0.07	
			% score >7		54 (aPD)					
			Beta coefficient		0.70 (HD)			ref.	0.52 to 0.92, *P* = 0.01	Propensity matched patients (all analyses)
			Beta coefficient		0.86 (aPD)			ref.	0.86 to 1.12, *P* = 0.24	

Table 4. *(continued)*

Study	PROM	Outcome domain	Effect estimate	Results dialysis patient group			Results conservative care	Statistical significance	Adjusted for
				Before start	*After start*	*Combined*	*Combined eGFR <10 mL/ eGFR><10 min/1.73 m²*		
Tan, 2017 [43]	POS-S renal	Symptom score	Mean at baseline[a]		9		9	Not reported	Not adjusted
		Symptom score	Mean change over 6 months		-7.6		-1.5	$P = 0.002$	
		Pain	% at baseline; % at 6 months		33; 25		88; 25	$P = 0.015$; $P = 0.10$	
		Shortness breath	% at baseline; % at 6 months		42; 8		63; 63	$P = 0.39$; $P = 0.01$	
		Weakness	% at baseline; % at 6 months		83; 50		50; 50	$P = 0.12$; $P = 0.99$	
		Nausea	% at baseline; % at 6 months		17; 0		0; 0	$P = 0.25$; n/a	
		Vomiting	% at baseline; % at 6 months		17; 0		0; 0	$P = 0.25$; n/a	
		Poor appetite	% at baseline; % at 6 months		50; 8		25; 25	$P = 0.29$; $P = 0.33$	
		Constipation	% at baseline; % at 6 months		25; 17		50; 38	$P = 0.27$; $P = 0.32$	
		Mouth problems	% at baseline; % at 6 months		0; 0		13; 25	$P = 0.23$; $P = 0.07$	
		Drowsiness	% at baseline; % at 6 months		17; 0		25; 40	$P = 0.67$; $P = 0.004$	
		Poor mobility	% at baseline; % at 6 months		25; 8		63; 63	$P = 0.10$; $P = 0.01$	
		Itching	% at baseline; % at 6 months		50; 8		38; 25	$P = 0.61$; $P = 0.33$	
		Difficulty sleeping	% at baseline; % at 6 months		58; 17		50; 38	$P = 0.73$; $P = 0.32$	
		Restless legs	% at baseline; % at 6 months		8; 8		25; 25	$P = 0.33$; $P = 0.33$	
		Feeling anxious	% at baseline; % at 6 months		25; 8		50; 25	$P = 0.27$; $P = 0.33$	
		Feeling depressed	% at baseline; % at 6 months		42; 0		13; 25	$P = 0.18$; $P = 0.07$	
		Skin changes	% at baseline; % at 6 months		17; 17		0; 25	$P = 0.25$; $P = 0.67$	
		Diarrhea	% at baseline; % at 6 months		0; 0		0; 0	n/a	

Table 4. *(continued)*

Study	PROM	Outcome domain	Effect estimate	Results dialysis patient group			Results conservative care	Statistical significance	Adjusted for
				Before start	*After start*	*Combined*	*Combined eGFR <10 mL/ eGFR><10 min/1.73 m²*		
Yong, 2009 [45]	Symptom list	Overall	Mean number		9.3		8.2	$P = 0.24$	Not adjusted
		Fatigue	%; intensity (NRS scale)		75; 5.5		69; 5.9	$P = 0.39$; $P = 0.90$	
		Cold aversion	%; intensity (NRS scale)		69; 5.5		78; 5.1	$P = 0.24$; $P = 0.12$	
		Pruritus	%; intensity (NRS scale)		66; 5.6		58; 4.3	$P = 0.34$; $P = 0.02$	
		Difficulty sleeping	%; intensity (NRS scale)		62; 5.4		49; 5.8	$P = 0.12$; $P = 0.11$	
		Lower torso weakness	%; intensity (NRS scale)		60; 5.3		58; 5.7	$P = 0.82$; $P = 0.10$	
		Skin changes	%; intensity (NRS scale)		55; 5.1		29; 4.4	$P = 0.003$; $P = 0.84$	
		Halitosis	%; intensity (NRS scale)		34; 4.4		18; 4.5	$P = 0.045$; $P = 0.27$	
		Sexual problem	%; intensity (NRS scale)		34; 6.8		9; 3.3	$P = 0.001$; $P = 0.04$	
		Dyspnea	%; intensity (NRS scale)		30; 4.4		47; 5.1	$P = 0.04$; $P = 0.60$	
		Change in taste	%; intensity (NRS scale)		19; 5.1		16; 3.3	$P = 0.57$; $P = 0.03$	
		Bloated abdomen	%; intensity (NRS scale)		28; 4.9		22; 3.5	$P = 0.48$; $P = 0.04$	
		Limb numbness	%; intensity (NRS scale)		50; 4.4		42; 3.8	$P = 0.37$; $P = 0.04$	
		Other[b]	%; intensity (NRS scale)		[b]		[b]	All $P > 0.05$[b]	
	BPI	Pain intensity scores	Worst pain (mean)		5.2		4.8	$P = 0.18$	
			Least pain (mean)		3.1		3.0	$P = 0.99$	
			Average pain (mean)		4.1		4.2	$P = 0.43$	
			Pain now (mean)		2.7		3.0	$P = 0.20$	

Table 4. *(continued)*
[a] Results were estimated from the reported figure.
[b] No significant differences in prevalence and intensity were found for dry mouth, cough, pain, loss of appetite, muscle cramp, dizziness, limb swelling, constipation, nausea, hearing impairment, and restless legs.
aPD, assisted peritoneal dialysis; BDI, Beck Depression Inventory (score range 0-63; higher scores represent higher symtom burden); BPI, Brief Pain Inventory (score range: 0-10, higher scores represent higher pain burden); CC, conservative care; choice D, patients who had chosen but not yet started dialysis; D, dialysis (patients treated with dialysis; modalities unspecified); eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); HADS, Hospital Anxiety and Depression Scale (score range: 0-21, higher scores represent higher symptom burden); HD, hemodialysis; KDQOL-SF, Kidney Disease Quality of Life-Short Form (79 items; score range: 0-100, higher scores represent lower symptom burden); KDQOL-36, Kidney Disease Quality of Life-Short Form (36 items; score range: 0-100, higher scores represent lower symptom burden); KPS, Karnofsky performance scale; mix D, mix of patients who had selected dialysis but not yet started dialysis and patients who were being treated with dialysis; MSAS-SF, Memorial Symptom Assessment Scale (higher scores represent higher symptom burden); n/a, not applicable; PD, peritoneal dialysis; POS-S renal, Palliative care Outcome Scale – Symptoms (Renal) (score range: 0-80, higher scores represent higher symptom burden); PROM, patient-reported outcome measure; ref., reference group; STAI-Y, State Trait Anxiety Inventory (higher scores represent higher anxiety burden).

DISCUSSION

This systematic review summarizes patient-reported HRQoL outcomes and symptoms among patients who chose either conservative care or a dialysis pathway for ESKD. We identified eleven observational cohort studies that were generally small-scale and of suboptimal study quality, being susceptible to selection bias and confounding. Patients who chose conservative care were generally older and less fit than patients who chose dialysis. Despite considerable clinical and methodological heterogeneity, the results on HRQoL and symptoms were broadly consistent across the studies. Physical health outcomes and symptom burden appeared to be worse in patients who chose conservative care compared with patients who chose dialysis but were not started yet. Similar physical health outcomes and symptom burden were observed between patients who chose conservative care compared with patients on dialysis. Mental health outcomes were also similar between patients who chose conservative care or dialysis, including before and after dialysis start. In patients who chose dialysis, the burden of kidney disease and impact on daily life increased after dialysis start.

Most studies on conservative care and dialysis focused on survival and showed an overall survival benefit in older patients who chose a dialysis pathway compared with conservative care [13, 14]. This survival benefit was, however, absent or limited in the oldest patients and patients with multiple comorbidities [13, 14]. Studies also

found that older patients who chose conservative care had lower treatment burden and hospitalization rates including at the end of life than patients who chose dialysis, both before and after dialysis start [46-49]. For example, one study observed that older patients who chose conservative care spent 4% of the days survived at or in hospital compared with 48% for patients on hemodialysis [46]. The need for more patient-relevant data on conservative care and dialysis is increasingly recognized [8, 20, 23, 50]. Such data could help to evaluate treatment effectiveness and inform the shared decision-making process by patients and clinicians, which is recommended as model to decide on preferred treatment for ESKD [8-10, 51-53]. The studies on HRQoL and symptoms, both major outcomes to patients and clinicians [15-19], extend the available patient-relevant data on both treatment pathways.

While heterogeneous, the results on HRQoL and symptoms were notably similar across the studies, which were mostly performed in patients above 65 years old. The studies therefore provide provisional but valuable insight whether conservative care in older patients has potential to achieve reasonable HRQoL outcomes and symptoms compared with a dialysis pathway. First, patients on both treatment pathways reported impaired physical health and a high symptom burden, stressing the need of improved supportive care in both pathways [8, 54-56]. Secondly, no distinct advantage on HRQoL outcomes and symptoms of one treatment pathway over the other could be identified when comparing both treatment pathways, particularly between patients who chose conservative care and patients on dialysis. An exception is the higher burden of kidney disease reported by patients who chose dialysis, especially after dialysis start, compared with patients who chose conservative care. These findings on HRQoL and symptoms support current guideline recommendations that in selected older patients conservative care might be a viable alternative to a dialysis pathway for ESKD [8-10].

Patients, their family, and clinicians are likely to have specific reasons to choose or recommend conservative care or a dialysis pathway [15, 16, 18]. An important consideration of the observational data on HRQoL and symptoms therefore is the risk of selection bias and confounding. Substantial differences in characteristics were observed between both patient groups, which may have resulted in a biased comparison of HRQoL outcomes and symptoms in the younger and likely more fit patients choosing dialysis compared with the older and less fit patients choosing conservative care. This, however, makes the similarities in HRQoL outcomes and symptoms between both patient groups

even more remarkable. Furthermore, younger and more well patients are in general more likely to complete HRQoL measures. We determined a high risk of incomplete outcome data in three studies [35, 36, 42], but it remains unclear whether more missing data were seen in older patients or other specific subgroups. Five studies adjusted for a set of confounders in multivariable analyses or by propensity-matching to better compare the effect of both treatment pathways itself [37-39, 41, 42], but residual confounding by unmeasured and unknown determinants is likely. Data on health status and frailty as assessed in a comprehensive geriatric assessment are associated with outcomes and might enable more accurate comparisons [6, 57, 58]. Such data could also improve outcome prediction and help identify modifiable risk factors [57, 59].

The validity of the used outcome measures in our patient population of interest, comprising older patients and patients on the relatively new treatment pathway of conservative care, is less clear [60-63]. Most studies used the Short Form-36 or Short Form-12 to assess HRQoL outcomes, which are well-validated in many populations and diseases including ESKD [20, 64, 65]. A recent validation study of the Short Form-36 in patients on conservative care, however, showed that the summary scores on physical and mental health (PCS and MCS) are more appropriate to use rather than the scores on individual subscales [60]. More validation studies are needed to specifically assess the validity and reliability of patient-reported outcome measures of HRQoL and symptoms in this growing older patient population.

Another methodological issue in the studies on HRQoL and symptoms is whether equivalent time points in conservative care and dialysis pathways were used for patient inclusion and outcome comparisons. Although all studies used eGFR thresholds, most studies compared outcomes in patients who chose conservative care with a mean eGFR above 10 mL/min/1.73 m^2 to patients on dialysis, which is generally started at an eGFR below 10 mL/min/1.73 m^2. Equivalent time points in both treatment pathways are necessary to avoid potential lead time bias in outcome comparisons [30]. While time of dialysis start and an equivalent in patients who chose conservative care enables evaluation of treatment itself, this time point ignores the period between treatment decision-making and actual dialysis start. Since patients could change their decision during this period [66], using time of dialysis start brings potential selection bias. For clinical practice, using time of treatment decision is more informative being better

applicable to patients during decision-making, although such data rather represent the results of a chosen treatment pathway than of treatment itself.

High-quality studies would be needed to confirm, and extend, current findings on HRQoL and symptoms in patients who chose conservative care or a dialysis pathway, including at different eGFR levels and both before and after dialysis start. Theoretically, a randomized controlled trial including intention-to-treat analysis could offer the best study design to deal with the limitations of current outcome data on both treatment pathways. In practice, however, such trials pose difficult ethical questions and might be difficult to perform [67]. One randomized controlled trial is currently ongoing in the United Kingdom [https://doi.org/10.1186/ISRCTN17133653]. Non-randomized studies should prospectively follow patients on both treatment pathways from an equivalent starting point with intention-to-treat analysis and reasonable adjustment for confounders. Standardization should be considered as a matter of importance to increase the efficacy of studies and patient input [68].

For HRQoL, both generic and kidney disease-specific domains provided relevant outcome data and should be further explored, including separate analyses per dialysis modality. For symptom burden, more insight is needed whether or not specific symptoms are more prevalent or severe in conservative care or a dialysis pathway. Two studies, for example, observed more dyspnea in patients on conservative care which might be a consequence of not being treated with dialysis [43, 45]. Patients should ideally be followed until the end of life to assess outcomes during the entire trajectory [69]. Finally, researchers and clinicians should develop and test best practices of both conservative care and integrated supportive care in dialysis pathways to improve care quality in patients with ESKD [8, 54-56].

In clinical practice, conservative care should become more available and appropriately offered as one of the possible treatment pathways for ESKD in older patients [17, 70, 71]. A dynamic shared decision-making process by the patient, the patient's family, and the healthcare team is needed. Such process should involve ongoing discussion and evaluation of what matters to the patient in order to decide on a treatment pathway for ESKD that fits best with the patient [18].

Strengths of our systematic review are its comprehensive search using broad search terms in multiple databases and that PRISMA guidelines were followed. We also carefully assessed whether studies included the population of interest, particularly for conservative care-like patient groups since many different terms were used. Our definition of conservative care was based on the consensus definition from KDIGO [8]. We focused on comparative studies in patients who had made a decision on treatment for ESKD. Outcomes in patients who postponed a decision and in patients with acute kidney injury need further research. A limitation might be our exclusion of non-English publications. No meta-analysis was performed due to the substantial clinical and methodological heterogeneity among the studies providing too limited homogeneous data on similar effect estimates with comparable adjustment for confounders.

Our systematic review demonstrated that in selected older patients conservative care has potential to achieve similar patient-reported HRQoL outcomes and symptoms compared with a dialysis pathway, although data were limited and of suboptimal quality. High-quality prospective studies are needed to confirm and extend the provisional findings on these patient-relevant outcomes. Considered together with evidence on survival and treatment burden [13, 14, 46-49], we conclude that conservative care could be a viable alternative to dialysis in selected older patients. Conservative care should therefore be part of the shared decision-making process by older patients and clinicians on preferred treatment for ESKD.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Search strategy and selection criteria

Search terms[a]	PubMed database: ("Renal Insufficiency, Chronic"[Mesh] OR ESRD[tiab] OR ESRF[tiab] OR ESKD[tiab] OR ESKF[tiab] OR ((end-stage[tiab] OR endstage[tiab] OR advanced[tiab] OR stage 4[tiab] OR stage 5[tiab] OR stage IV[tiab] OR stage V[tiab]) AND (CKD[tiab] OR kidney disease[tiab] OR renal disease[tiab] OR kidney failure[tiab] OR renal failure[tiab] OR kidney insufficiency[tiab] OR renal insufficiency[tiab]))) AND ("Renal replacement therapy"[Mesh] OR renal replacement therap*[tiab] OR dialysis[tiab] OR kidney replacement therap*[tiab] OR hemodialysis[tiab] OR haemodialysis[tiab] OR hemofiltration[tiab] OR haemofiltration[tiab] OR hemodiafiltration[tiab] OR haemodiafiltration[tiab] OR HD[tiab] OR PD[tiab] OR CAPD[tiab] OR CCPD[tiab]) AND ("Palliative Care"[Mesh] OR "Palliative Medicine"[Mesh] OR "Watchful Waiting"[Mesh] OR conservative[tiab] OR palliative[tiab] OR nondialytic[tiab] OR non-dialytic[tiab] OR supportive care[tiab] OR non-dialysis[tiab] OR watchful waiting[tiab])
Inclusion criteria	• Patients with advanced chronic kidney disease (stage 4/5) • Comparison of non-dialytic conservative care *versus* a dialysis pathway • Conservative care: patients in whom a decision was made to treat end-stage kidney disease conservatively, including all interventions except dialysis, with the intention to provide it until death (not just to postpone dialysis; and irrespective of how or by whom the decision was made) • Dialysis pathway: patients in whom a decision was made to treat end-stage kidney disease with dialysis, including patients who chose but were not yet started on dialysis, and patients who started or were on dialysis • Study design: randomized controlled trials, observational studies including prospective cohorts, retrospective cohorts, case-control studies, or case reports with >5 patients included per patient group • Outcomes of interest: patient-reported outcomes on health-related quality of life and/or symptoms
Exclusion criteria	• Patients with acute kidney injury • No comparison group: not including both a conservative care patient group and dialysis patient group • No treatment decision yet: patients with advanced chronic kidney disease in whom no decision was made on intended treatment for end-stage kidney disease • No outcomes of interest, including: patient education, pharmacokinetics, economic evaluations, and studies on treatment decision-making • No original research, including: reviews, letters, opinion papers, abstracts only, and study protocols • Pediatric (<18 years) • Not human • Not English
Searches performed up to October 1st, 2019, in PubMed, EMBASE, The Cochrane Library, CINAHL Plus, and PsycINFO.	

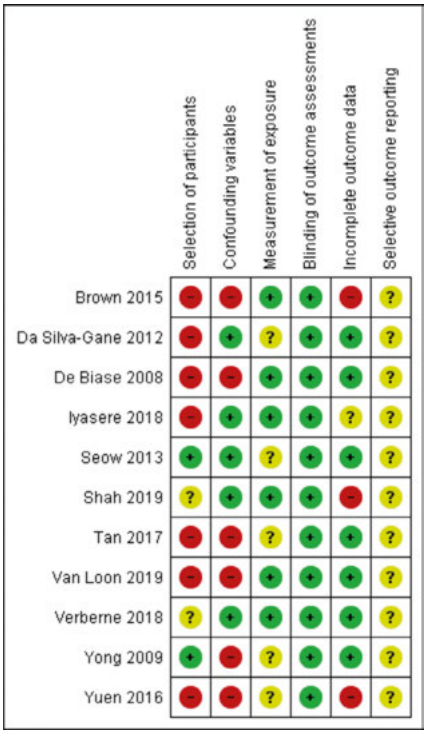
[a] A proposal on search terms and databases to be searched was reviewed and pilot tested by an external clinical librarian.

Supplementary Table S2. Results of contact with study authors to clarify their conservative care-like patient group

Study	Response	Study authors' explanation of their non-dialysis or conservative care-like patient group	Decision on inclusion
Almutary, 2016 [1]	Yes	No treatment decision yet (patients with stage 4 and 5 chronic kidney disease; considered too early to make a decision)	Excluded
Bonner, 2018 [2]	Yes	Mix of patients with stage 4 and 5 chronic kidney disease (considered too early to make a decision) and patients with stage 5 chronic kidney disease who had chosen to be treated conservatively; no subgroup analysis	Excluded
Buemi, 2018 [3]	Yes	Mix of patients with stage 4 and 5 chronic kidney disease (majority; unknown if a treatment decision had been made or considered too early to make a decision) and patients who had chosen to be treated conservatively (almost negligible number); no subgroup analysis	Excluded
Gutiérrez Sánchez, 2017 [4]	Yes	Most patients had not yet started dialysis, or had made no treatment decision yet	Excluded

1. Almutary H, Bonner A, Douglas C. Which patients with chronic kidney disease have the greatest symptom burden? A comparitive study of advanced CKD stage and dialysis modality. J Ren Care. 2016;42(2):73-82.
2. Bonner A, Chambers S, Healy H, et al. Tracking patients with advanced kidney disease in the last 12 months of life. J Ren Care. 2018;44(2):115-22.
3. Buemi M, Bruno A, Cordova F, et al. Negative Emotions in End-Stage Renal Disease: Are Anxiety Symptoms Related to Levels of Circulating Catecholamines? Curr Psychol. 2018;39:729-735.
4. Gutiérrez Sánchez D, Leiva-Santos JP, Cuesta-Vargas AI. Symptom Burden Clustering in Chronic Kidney Disease Stage 5. Clin Nurs Res. 2017;28(5):583-601.

Supplementary Table S3. Risk of bias assessment per included study, the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) [1]



+, high risk of bias; -, low risk of bias; ?, unclear risk of bias
(A) Selection of participants, to assess whether the patient groups were the same population group and whether the maximum number of eligible patients was included per patient group.
(B) Confounding variables, to assess whether confounding variables were adequately confirmed and considered including multivariable models adjusting for likely possible confounders.
(C) Measurement of exposure, to assess whether baseline data and outcome data were collected from trustworthy sources.
(D) Blinding of outcome assessments. Given our outcomes of interest were patient-reported, this was considered low risk for all studies.
(E) Incomplete outcome data, to assess how missing data and loss-to-follow-up were handled. Studies were deemed high risk if >10% of patients were excluded due to missing data.
(F) Selective outcome reporting, to assess whether outcomes were described as planned per published protocol. If there was no available protocol it was deemed unclear.

1. Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol. 2013;66 (4):408-14.

Supplementary Table S4. Baseline and follow-up results on health-related quality of life per study

Study	PROM	Outcome domain	Effect estimate	Statistical significance	Adjusted for
Brown, 2015 [1]	SF-36	PCS score	Baseline (mean), Choice D vs. CC = 38 vs. 29	$P < 0.001$	Not adjusted
			After 12 months, Choice D vs. CC = 55/4/41% vs. 63/16/21% worse/stable/improved	$P = 0.12$	
		MCS score	Baseline (mean), Choice D vs. CC = 50 vs. 46	$P = 0.06$	
			After 12 months, Choice D vs. CC = 45/2/53% vs. 42/5/53% worse/stable/improved	$P = 0.78$	
Yuen, 2016 [2]	SF-36	Physical function	Mix D vs. CC (mean) = 88.7 vs. 81.2	$P < 0.001$	Not adjusted
		Role physical	Mix D vs. CC (mean) = 81.8 vs. 75.5	$P = 0.77$	
		Bodily pain	Mix D vs. CC (mean) = 83.5 vs. 78.9	$P = 0.12$	
		General health	Mix D vs. CC (mean) = 53.9 vs. 50.3	$P < 0.001$	
		Vitality	Mix D vs. CC (mean) = 61.5 vs. 60.4	$P = 0.94$	
		Social function	Mix D vs. CC (mean) = 92.9 vs. 92.2	$P = 0.49$	
		Role emotional	Mix D vs. CC (mean) = 77.7 vs. 77.9	$P = 0.37$	
		Mental health	Mix D vs. CC (mean) = 74.5 vs. 75.7	$P = 0.008$	
Da Silva-Gane, 2012 [3]	SF-36 SWLS	PCS score	Baseline (mean), Choice HD vs. Choice PD vs. CC = 25.2 vs. 30.1 vs. 18.0	$P < 0.001$	Age, sex, comorbidity score, KPS score, propensity score (mean changes)
			Change per month (mean), entire cohort = +0.04	± 0.17, "non-significant"	
			Change after dialysis start (mean), HD/PD group = +0.49	± 1.7, $P = 0.53$	
		MCS score	Baseline (mean), Choice HD vs. Choice PD vs. CC = 47.6 vs. 45.9 vs. 49.9	"Non-significant"	
			Change per month (mean), entire cohort = 0.12	± 0.32, $P < 0.05$	
			Change after dialysis start (mean), HD/PD group = -0.68	± 5.84, $P = 0.53$	
		Satisfaction with life scale	Baseline (mean), Choice HD vs. Choice PD vs. CC = 21.7 vs. 22.5 vs. 23.2	"Non-significant"	
			Change per month (mean), entire cohort = 0.02	± 0.11, "non-significant"	
			Change after dialysis start (mean), HD/PD group = -1.84	± 4.50, $P = 0.01$	
Seow, 2013 [4]	KDQOL-SF	PCS score	Baseline (figure), Choice D vs. CC = median 33 vs. 34[a]	Not reported	Age, comorbidity score, KPS score, primary renal disease, change in eGFR (b coefficients)
			Change per month (b coefficient), Choice D vs. D vs. CC = -0.29 vs. -0.30 vs. -0.10	$P = 0.07$	
			Difference at dialysis start (b coefficient), D group = +1.72	-0.57 to 4.01, $P = 0.14$	
		MCS score	Baseline (figure), Choice D vs. CC = median 43 vs. 52[a]	Not reported	
			Change per month (b coefficient), Choice D vs. D vs. CC = +0.01 vs. -0.09 vs. +0.13	$P = 0.89$	
			Difference at dialysis start (b coefficient), D group = -0.26	-3.39 to 2.86, $P = 0.87$	
		Effects of kidney disease	Change per month (b coefficient), Choice D vs. D vs. CC = -0.34 vs. -0.25 vs. +0.30	$P = 0.01$	
			Difference at dialysis start (b coefficient), D group = -3.86	-0.74 to -0.31, $P = 0.03$	
		Burden of kidney disease	Change per month (b coefficient), Choice D vs. D vs. CC = -0.58 vs. -0.65 vs. +0.54	$P < 0.001$	
			Difference at dialysis start (b coefficient), D group = -25.11	-32.2 to -18.1, $P < 0.001$	

Supplementary Table S4. *(continued)*

Study	PROM	Outcome domain	Effect estimate	Statistical significance	Adjusted for
Verberne, 2018 [5, 6]	KDQOL-SF	PCS score[b]	Choice D vs. CC (mean) = 38.3 vs. 30.9	$P < 0.01$	Sex, way of administration (b coefficients) Similar results when also adjusted for age and comorbidity score
			Choice D vs. CC (b coefficient) = +6.61	1.79 to 11.43, $P < 0.01$	
			D vs. CC (mean) = 34.2 vs. 30.9	$P = 0.38$	
			D vs. CC (b coefficient) = +2.20	−2.79 to 7.20, $P = 0.38$	
		MCS score[b]	Choice D vs. CC (mean) = 52.8 vs. 47.5	$P = 0.17$	
			Choice D vs. CC (b coefficient) = +6.45	1.48 to 11.41, $P = 0.01$	
			D vs. CC (mean) = 50.5 vs. 47.5	$P = 0.58$	
			D vs. CC (b coefficient) = -0.58	−5.80 to 4.64, $P = 0.83$	
		Effects of kidney disease	Choice D vs. CC (median) = 92.9 vs. 82.7	$P = 0.03$	
			D vs. CC (median) = 85.7 vs. 82.7	$P = 0.35$	
		Burden of kidney disease	Choice D vs. CC (median) = 75.0 vs. 75.0	$P = 0.70$	
			D vs. CC (median) = 43.8 vs. 75.0	$P = 0.001$	
De Biase, 2008 [7]	SF-36	Physical function	HD vs. CC (mean) = 45 vs. 28	Not reported	Not adjusted
		Role physical	HD vs. CC (mean) = 15 vs. 25		
		Bodily pain	HD vs. CC (mean) = 62 vs. 47		
		General health	HD vs. CC (mean) = 46 vs. 41		
		Vitality	HD vs. CC (mean) = 51 vs. 47		
		Social function	HD vs. CC (mean) = 75 vs. 77		
		Role emotional	HD vs. CC (mean) = 60 vs. 40		
		Mental health	HD vs. CC (mean) = 67 vs. 67		
Iyasere, 2018 [8]	SF-12	PCS score	HD vs. aPD vs. CC (median) = 29.2 vs. 30.8 vs. 28.9	$P = 0.62$	Age, sex, comorbidity score, frailty score, dialysis vintage (beta coefficients) Propensity matched patients (all analyses)
			HD vs. CC (beta coefficient) = 1.08	0.89 to 1.29, $P = 0.45$	
			aPD vs. CC (beta coefficient) = 1.20	1.00 to 1.45, $P = 0.05$	
		MCS score	HD vs. aPD vs. CC (median) = 49.9 vs. 50.2 vs.46.3	$P = 0.68$	
			HD vs. CC (beta coefficient) = 1.03	0.87 to 1.22, $P = 0.71$	
			aPD vs. CC (beta coefficient) = 1.07	0.90 to 1.27, $P = 0.44$	
	IIRS	Illness intrusiveness rating scale	HD vs. aPD vs. CC (median) = 31.0 vs. 32.0 vs. 30.5	$P = 0.79$	
			HD vs. CC (beta coefficient) = 1.17	0.93 to 1.48, $P = 0.19$	
			aPD vs. CC (beta coefficient) = 1.11	0.86 to 1.42, $P = 0.42$	

Supplementary Table S4. *(continued)*

Study	PROM	Outcome domain	Effect estimate	Statistical significance	Adjusted for
Shah, 2019 [9]	KDQOL-36	PCS score	D vs. CC (mean) = 31.2 vs. 34.3	"Non-significant"	Age, sex, country, education, health insurance (b coefficients)
			D vs. CC (b coefficient) = -3.17	-7.61 to 1.27, $P = 0.16$	
		MCS score	D vs. CC (mean) = 47.7 vs. 46.6	"Non-significant"	
			D vs. CC (b coefficient) = -2.41	-7.66 to 2.84, $P = 0.37$	
		Effects of kidney disease	D vs. CC (mean) = 64.2 vs. 81.3	$P < 0.001$	
			D vs. CC (b coefficient) = -16.49	-25.98 to -6.99, $P < 0.001$	
		Burden of kidney disease	D vs. CC (mean) = 34.7 vs. 62.8	$P < 0.001$	
			D vs. CC (b coefficient) = -28.59	-41.77 to -15.42, $P < 0.001$	
Van Loon, 2019 [10]	EQ-5D-3L	EQ-5D Index score	Baseline (mean), D vs. CC = 0.82 vs. 0.77	$P = 0.05$	Not adjusted
			Change after 6 months, D = +0.026	$P = 0.10$	
			Change after 6 months, CC = -0.047	$P < 0.01$	
			Difference between D and CC	$P < 0.01$	
			% worse/stable/improved, eGFR<10 (subgroup), D vs. CC = 21/32/47 vs. 41/48/11	$P = 0.01$	
			% worse/stable/improved, eGFR≥10 (subgroup), D vs. CC = 33/31/36 vs. 35/44/21	$P = 0.27$	
			% worse/stable/improved, <80 years (subgroup), D vs. CC = 25/30/44 vs. 35/47/18	$P = 0.08$	
			% worse/stable/improved, ≥80 years (subgroup), D vs. CC = 21/34/45 vs. 38/45/17	$P = 0.02$	
		EQ-5D self-rated health score (scale 0 – 10)	Baseline (mean), D vs. CC = 6.3 vs. 6.3	$P = 0.91$	
			Change after 6 months, D = +0.3	$P < 0.01$	
			Change after 6 months, CC = -0.4	$P < 0.01$	
			Difference between D and CC	$P < 0.01$	
		Mobility	Baseline (% impaired), D vs. CC = 58 vs. 71	$P = 0.04$	
			After 6 months (% impaired), D vs. CC = 55 vs. 78	$P < 0.01$	
		Self-care	Baseline (% impaired), D vs. CC = 27 vs. 38	$P = 0.05$	
			After 6 months (% impaired), D vs. CC = 24 vs. 41	$P < 0.01$	
		Usual activities	Baseline (% impaired), D vs. CC = 58 vs. 56	$P = 0.73$	
			After 6 months (% impaired), D vs. CC = 53 vs. 63	$P = 0.16$	
		Pain/discomfort	Baseline (% impaired), D vs. CC = 51 vs. 69	$P < 0.01$	
			After 6 months (% impaired), D vs. CC = 44 vs. 66	$P < 0.01$	
		Anxiety/depression	Baseline (% impaired), D vs. CC = 31 vs. 24	$P = 0.22$	
			After 6 months (% impaired), D vs. CC = 19 vs. 24	$P = 0.42$	

Supplementary Table S4. *(continued)*

Study	PROM	Outcome domain	Effect estimate	Statistical significance	Adjusted for
Yong, 2009 [11]	SF-36	Physical function	D vs. CC (mean) = 55.9 vs. 43.8	Not reported	Not adjusted
		Role physical	D vs. CC (mean) = 42.5 vs. 53.3		
		Bodily pain	D vs. CC (mean) = 75.2 vs. 72.8		
		General health	D vs. CC (mean) = 38.2 vs. 42.4		
		Vitality	D vs. CC (mean) = 51.2 vs. 49.0		
		Social function	D vs. CC (mean) = 65.8 vs. 73.6		
		Role emotional	D vs. CC (mean) = 50.5 vs. 68.9		
		Mental health	D vs. CC (mean) = 67.1 vs. 73.5		

[a] Results were estimated from the reported graphical figures.

[b] Results on the PCS and MCS were included from a reanalysis in which the same scoring algorithm as in similar studies was used (Verberne, 2019 [6]).

aPD, assisted peritoneal dialysis; CC, conservative care; choice D, patients who had chosen but not yet started dialysis; D, dialysis (patients treated with dialysis; modalities unspecified); eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); EQ-5D-3L, EuroQOL-5D-3L (score of 1 is perfect health in EQ-5D Index); HD, hemodialysis; HRQoL, health-related quality of life; IIRS, Illness intrusiveness rating scale (score range: 13-91, higher scores represent more illness intrusion); KDQOL-SF, Kidney Disease Quality of Life-Short Form (79 items, including the SF-36 and 8 kidney disease-specific domains; score range: 0-100, higher scores represent better quality of life); KDQOL-36, Kidney Disease Quality of Life-Short Form (36 items, including the SF-12 and 3 kidney disease-specific domains; score range: 0-100, higher scores represent better quality of life); KPS, Karnofsky performance scale; MCS, Mental Component Summary score (score range: 0-100, higher scores represent better quality of life); mix D, mix of patients who had selected dialysis but not yet started dialysis and patients who were being treated with dialysis; PCS, Physical Component Summary score (score range: 0-100, higher scores represent better quality of life); PD, peritoneal dialysis; PROM, patient-reported outcome measure; SF-12, Short Form-12; SF-36, Short Form-36; SWLS, Satisfaction with Life Scale (score range: 5-35, higher scores represent higher satisfaction with life).

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