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A Review of the Costs and Cost Effectiveness of Interventions in Chronic Kidney Disease

Implications for Policy

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Abstract

Given rising healthcare costs and a growing population of patients with chronic kidney disease (CKD), there is an urgent need to identify health interventions that provide good value for money.

For this review, the English-language literature was searched for studies of interventions in CKD reporting an original incremental cost-utility (cost per QALY) or cost-effectiveness (cost per life-year) ratio. Published cost studies that did not report cost-effectiveness or cost-utility ratios were also reviewed. League tables were then created for both cost-utility and cost-effectiveness ratios to assess interventions in patients with stage 1–4 CKD, waitlist and transplant patients and those with end-stage renal disease (ESRD). In addition, the percentage of cost-saving or dominant interventions (those that

save money and improve health) was compared across these three disease categories.

A total of 84 studies were included, contributing 72 cost-utility ratios, 20 cost-effectiveness ratios and 42 other cost measures. Many of the interventions were dominant over the comparator, indicating better health outcomes and lower costs. For the three disease categories, the greatest number of dominant or cost-saving interventions was reported for stage 1–4 CKD patients, followed by waitlist and transplant recipients and those with ESRD (91%, 87% and 55% of studies reporting a dominant or cost-saving intervention, respectively).

There is evidence of opportunities to lower costs in the treatment of patients with CKD, while either improving or maintaining the quality of care. In order to realize these cost savings, efforts will be required to promote and effectively implement changes in treatment practices.

Over the past several years, chronic kidney disease (CKD) has become a disease of increasing and societal importance, affecting as many as one in eight US adults over the period 1999–2004.[1] Since 2002, CKD has been classified into five stages, with stages reflecting the estimated glomerular filtration rate (eGFR, calculated from the serum creatinine level) and evidence of kidney damage (most commonly assessed as albuminuria or proteinuria).[2] Stage 5 CKD indicates kidney failure; if treated with kidney replacement therapy (dialysis or transplantation), this is often referred to as end-stage renal disease (ESRD). The prevalence rate of ESRD in the US was estimated at 163 per 100 000 individuals in 2006, a 15% increase over 2000.[3] Both in the US and worldwide, the prevalence of ESRD continues to rise,[4] likely reflecting changing demographics (including an aging population with increasingly common co-morbid diseases, such as hypertension and diabetes mellitus) as well as improved survival among individuals with ESRD. The direct financial cost of ESRD is substantial, with the US Medicare programme spending $US23 billion on ESRD care in 2006, representing an expenditure of 7.4% of the Medicare budget for just 1.1% of the Medicare population.[3] Reflecting the expense associated with kidney replacement therapy, costs, and therefore cost effectiveness, of CKD therapies are largely driven by the ability to slow progression to kidney failure and limit time spent receiving dialysis.[5,6]

Better approaches to the management of both non-dialysis CKD and ESRD may offer the potential to slow the growth in costs or may otherwise offer 'value for money' in terms of improving clinical outcomes at a reasonable cost. This emphasis is increasingly important for providers in light of the new ESRD Prospective Payment System (PPS), a complex bundled reimbursement system for dialysis treatment that was introduced for US Medicare patients on 1 January 2011, which provides more incentives to offer cost-effective services.[7] In addition, other health authorities (such as the UK National Institute for Health and Clinical Excellence [NICE]) now require evidence of cost effectiveness to reimburse selected drugs and other technologies. Many health plans also now request evidence of both clinical and economic value for new therapies.[8] Although cost effectiveness is not officially considered in US reimbursement decisions, passage of the American Recovery and Reinvestment Act of 2009 (ARRA) signalled the Government's clear intent to provide researchers, clinicians, policy makers and payers with more information on the comparative effectiveness of treatment.[9]

The existing body of literature related to cost effectiveness in kidney disease mostly consists of reviews of individual pharmaceutical therapies[10-13] and treatment strategies.[14] The purpose of this review was to assess cost effectiveness across the broad range of interventions for the CKD population and identify interventions that may

benefit from further assessment. More studies of the cost effectiveness of interventions can provide a basis from which future decisions about use of these treatment strategies may be made. This review was designed to identify interventions that provide reasonable value as well as those with the potential to lower costs and improve the quality of care (so called 'dominant' interventions).

1. Literature Search

1.1 Methods

A comprehensive electronic search was performed of the English-language literature, limited to studies of humans, with abstracts available, focusing on those published over the period 1998–2008, inclusive. Letters to the editor, editorials, interviews and case reports were excluded. MeSH, EMTREE and free-text search terms used in PubMed and EMBASE searches included chronic kidney failure, co-morbidity, burden, complications, cost of illness, cost-benefit analysis (a term that encompasses cost effectiveness in PubMed), and economics and costs. In addition, we also searched the Tufts Medical Center Cost-Effectiveness Analysis (CEA) Registry[15] and the UK NHS Economic Evaluations Database.[16] Because our focus was on treatments or policy (e.g. reimbursement, population screening for CKD), studies were excluded if they were limited to epidemiology, kidney disease as a secondary topic, biochemistry or methods (e.g. validation of a quality-of-life [QOL] questionnaire). After abstract review, the full texts of studies selected for inclusion were critically reviewed and summarized in terms of population, intervention and comparator, methods used and results.

Four authors initially screened approximately 650 titles obtained from the searches outlined above, resulting in a list of approximately 300 potentially relevant abstracts (figure 1). In addition, two physicians (Dr Mark Friedman and Dr Daniel Weiner) further screened the abstracts for relevance and other study inclusion criteria. Dr Friedman is a general internist and Medical Director at Boston Health Economics and Dr Weiner is Associate Medical Director at Dialysis Clinic, Inc., Boston (MA, USA), and a professor at Tufts Medical School. A total of 49 studies reporting original cost-effectiveness/cost-utility ratios were included, providing 72 cost-utility ratios (CUR) and 20 cost-effectiveness ratios (CER) for CKD interventions. An additional 35 studies provided cost data without CUR/CER.

'League tables' or ranked listings were then created for CURs (incremental cost per QALY

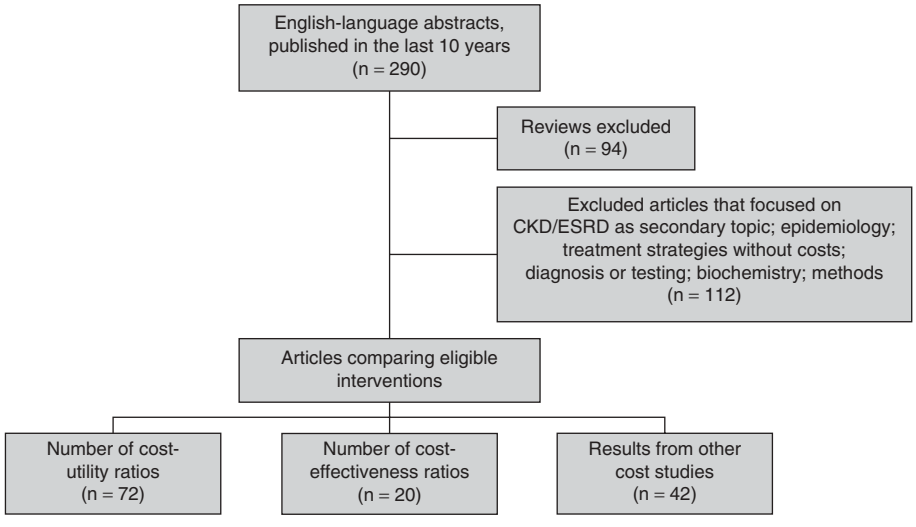

Fig. 1. Study selection process. **CKD** = chronic kidney disease; **ESRD** = end-stage renal disease.

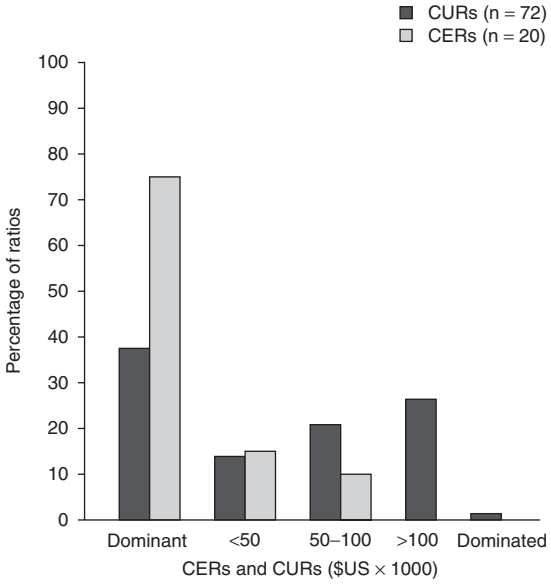

Fig. 2. Summary of cost-effectiveness ratios (CERs; incremental cost per life-year) and cost-utility ratios (CURs; incremental cost per QALY).

gained), CERs (incremental cost per life-year [LY] gained) and other cost analyses. Only base-case ratios were abstracted into league tables. In cases where no base case was stated, any ratios derived from a different population, intervention, comparator or perspective (societal or healthcare payer) were considered separate ratios and abstracted. Where multiple time horizons were used, only ratios for the longest time horizon reported were included in the league tables. These methods are based on the same criteria used by reviewers for the Tufts Medical Center CEA Registry.[15] All currencies were converted to $US and adjusted to 2008 constant values using the Medical Care Consumer Price Index (amounts reported in the text are rounded to the nearest $US100). If authors reported both discounted and undiscounted estimates, we used discounted estimates. We grouped studies with CURs or CERs into the following categories: dominant (better outcomes and lower costs); ratio <$US50 000; ratio $US50 000–100 000; ratio >$US100 000; and dominated (worse outcomes and higher costs).

In analysing the studies that did not report a cost per LY or QALY, we determined whether the intervention presented in the study improved clinical outcomes, worsened clinical outcomes or whether this was not reported. We then standardized costs or cost savings, where possible, to per person per year estimates and ranked the studies in order from most to least dollars saved.

1.2 Results

The majority of reported CERs were dominant (75%), while 38% of CURs were dominant; 15% of CERs and 14% of CURs were less than $US50 000; 10% of CERs and 21% of CURs were between $US50 000 and $US100 000; no CERs and 26% of CURs were greater than $US100 000 (figure 2). No reported CERs and only 1% of CURs were dominated (worse outcomes and higher costs). When the studies were grouped into three clinically relevant categories – stage 1–4 CKD, transplant and ESRD – the percentage of studies that reported a dominant or cost-saving intervention was highest in the CKD stages 1–4 population (91%), followed by the kidney transplant population (87%) and lastly ESRD (55%) [figure 3].

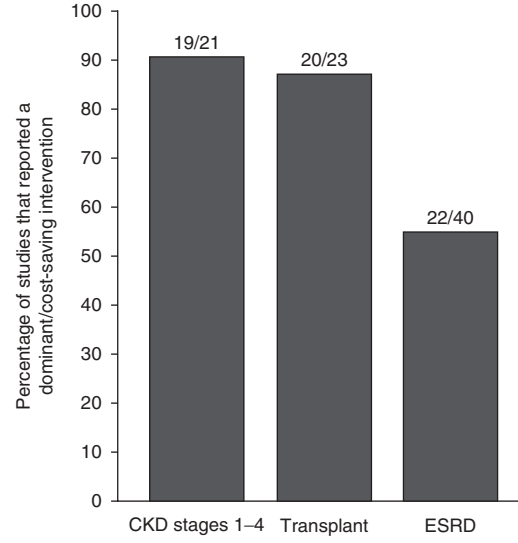

Fig. 3. Percentage of studies that reported a dominant/cost-saving intervention by patient population. Ratios above each bar indicate the number of studies reporting a dominant/cost-saving intervention in each population over the total number of studies reporting a cost-effectiveness ratio, cost-utility ratio or other cost measure. **CKD** = chronic kidney disease; **ESRD** = end-stage renal disease.

Table I. League table of cost-utility ratios (CURs [incremental cost per QALY])[a] in kidney disease

Study (pt population category)	Description	Time horizon (y)[b]	Perspective, country	CUR
Boulware et al.[17] (CKD)	Annual screening for proteinuria vs current practice (no screening of this population) in pts aged 50 y with diabetes	Lifetime	Societal, US	Dominant
Clark et al.[18] (CKD)	Programme to pay for ACE-I therapy vs no payment programme in pts with type 1 diabetes and overt proteinuria	21	Insurer, Canada	Dominant
Cleemput et al.[19] (transplant)	Kidney transplant vs dialysis in kidney transplant candidates	Lifetime	Societal, Belgium	Dominant
Douzdjian et al.[20] (transplant)	Kidney transplant from a cadaver vs dialysis in pts with type 1 diabetes and ESRD, base case assuming graft failure occurs at y 3	5	Insurer, US	Dominant
	Kidney transplant from a living donor vs dialysis in pts with type 1 diabetes and ESRD, base case assuming graft failure occurs at y 3	5	Insurer, US	Dominant
Gonzalez-Perez et al.[21] (ESRD)	Home HD vs hospital HD in HD pts	10	Insurer, UK	Dominant
Hogan et al.[22] (CKD)	Routine antihypertensive tx plus benazepril vs routine antihypertensive tx plus PL in pts with progressive renal insufficiency whose hypertension was managed with agents other than ACE-Is	7	Insurer, US	Dominant
Kontodimopoulos and Niakas[23] (transplant)	Transplant vs HD in ESRD pts	Lifetime	Insurer, Greece	Dominant
	Transplant vs PD in ESRD pts	Lifetime	Insurer, Greece	Dominant
Lindsay[24] (transplant)	Nocturnal HD (5–6 d/wk for 6–8 h) vs conventional dialysis (3×/wk in-centre) in ESRD pts aged ≥18 y, on dialysis ≥3 mo	3	Insurer, UK	Dominant
	Daily dialysis (5–6 d/wk for 1.5–2.5 h) vs conventional dialysis (3×/wk in-centre) in ESRD pts aged ≥18 y, on dialysis ≥3 mo	3	Insurer, UK	Dominant
Matas and Schnitzler[25] (transplant)	Kidney transplant vs dialysis in dialysis pts on the transplant wait list	20	Insurer, US	Dominant
McEwan et al.[26] (transplant)	Sirolimus vs ciclosporin in pts with immunosuppression after kidney transplant in the UK	20	Unstated, UK	Dominant
McEwan et al.[27] (transplant)	Sirolimus vs tacrolimus in kidney transplant recipients in the UK	20	Payer, UK	Dominant
McFarlane et al.[28] (ESRD)	Intensive home nocturnal HD for about 7 h approximately 6 nights a wk vs in-centre HD in demographically similar pts in Canada	14	Unstated, Canada	Dominant
McFarlane et al.[29] (ESRD)	Home nocturnal HD as initial modality vs pts treated with in-centre HD in prevalent dialysis pts, including both transplant eligible and ineligible pts	Lifetime	Insurer, US	Dominant
McLaughlin et al.[30] (transplant)	Routine use of high-resolution flow cytometry cross-matching and solid-phase screening vs SS alone in recipients of primary deceased donor kidney transplants aged <70 y	25	Payer, Canada	Dominant
Mendeloff et al.[31] (transplant)	Cadaveric donor kidney transplant vs dialysis in ESRD pts	Unstated	Insurer, US	Dominant
Mutinga et al.[32] (transplant)	Removing HLA-B matching from the deceased donor kidney allocation schema vs HLA-B matching between donor and potential recipient of a kidney in minority pts in the US awaiting kidney transplant	20	Unstated, US	Dominant

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Table I. Contd

Study (pt population category)	Description	Time horizon (y)[b]	Perspective, country	CUR
Palmer et al.[33] (CKD)	Nephropathy screening and tx vs no screening in hypertensive pts with type 2 diabetes who have nephropathy in France	Lifetime	Payer, France	Dominant
Roels et al.[34] (transplant)	Cadaveric transplant vs dialysis in ESRD pts	20	Insurer, Germany	Dominant
Rosen et al.[35] (CKD)	Medicare first-dollar coverage of ACE-Is vs current practice in all Medicare beneficiaries with diabetes, aged ≥65 y, half with kidney disease; societal perspective	Lifetime	Medicare, US	Dominant
Rosen et al.[35] (CKD)	Medicare first-dollar coverage of ACE-Is vs current practice in all Medicare beneficiaries with diabetes, aged ≥65 y, half with kidney disease; Medicare perspective	Lifetime	Medicare, US	Dominant
Schweitzer et al.[36] (transplant)	'Transplant' policy vs 'discard' (i.e. use vs discard kidneys from donors considered at high risk for HIV or HCV infection) policy in a cohort of pts aged 50 y on HD, awaiting a deceased donor kidney transplant	20	Payer, US	Dominant
Sennfalt et al.[37] (ESRD)	PD as initial modality vs HD as initial modality in incident dialysis pts aged ≥21 y	5	Societal, Sweden	Dominant
Takahashi et al.[38] (CKD)	Tx with AST-120, an oral adsorbent used to remove uraemic toxins vs PL in nondiabetic pts with serum creatinine levels 5–8 mg/dL	3	Insurer, Japan	Dominant
Whiting et al.[39] (transplant)	Cadaveric kidney transplantation vs dialysis in dialysis pts on the transplant wait list	20	Insurer, Canada	Dominant
Klarenbach et al.[40] (CKD)	Haemofiltration vs saline infusion in men aged 70 y with CKD, receiving contrast angiography, at high risk for contrast nephropathy	1	Insurer, Canada	4400
Manns et al.[41] (ESRD)	Synthetic dialyzer vs cellulose dialyzer; cost of the intervention (dialyzer) only, excludes cost of dialysis and transplantation; in male HD pts aged 60 y	Lifetime	Insurer, Canada	5200
Gonzalez-Perez et al.[21] (ESRD)	Home HD vs satellite HD in HD pts	10		6700
Jassal et al.[42] (transplant)	Cadaveric renal transplantation with no wait vs continued dialysis in non-diabetic dialysis pts aged 65 y who would have to wait ≥2 y for a cadaveric transplant	Lifetime	Insurer, US	21 700
Boulware et al.[17] (CKD)	Annual screening for proteinuria vs current practice (no screening of this population) in pts aged 50 y with hypertension	Unstated	Societal, US	23 700
Palmer et al.[43] (CKD)	Screening (dipstick testing) and tx (irbesartan and conventional antihypertensives) for nephropathy vs no screening, tx with conventional antihypertensives in a hypothetical cohort of pts with type 2 diabetes and hypertension	25	Insurer, US	27 900
Jassal et al.[42] (transplant)	Living donor kidney transplant with no wait vs continued dialysis in non-diabetic dialysis pts aged 65 y who would have to wait ≥2 y for a cadaveric transplant	Lifetime	Insurer, US	32 900

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Table I. Contd

Study (pt population category)	Description	Time horizon (y)[b]	Perspective, country	CUR
Glenngard et al.[44] (ESRD)	EPO + RBCT vs RBCT alone in RRT pts on PD	Lifetime	Provider, Sweden	41 000
Cleemput et al.[19] (transplant)	Adherence vs non-adherence to immunosuppressives in kidney transplant candidates	Lifetime	Societal, Belgium	45 000
Lee[45] (ESRD)	Starting dialysis when eGFR drops below 7.5 plus an additional 0.7 mL/min/1.73 m^2 for each 1 point of Charlson morbidity score <10 (significant delay relative to current practice) vs no dialysis in ESRD pts	Lifetime	Unstated, US	49 600
Brennan et al.[46] (ESRD)	8-wk trial of LC, if successful continue LC tx, otherwise switch back to tx with CC only vs CC for all in ESRD pts with hyperphosphataemia not adequately maintained on CC	Lifetime	Insurer, UK	51 900
Douzdjian et al.[20] (transplant)	Simultaneous pancreas-kidney transplant vs kidney transplant only, from a living donor in pts with type 1 diabetes and ESRD, base case assuming graft failure occurs at y 3	5	Insurer, US	73 300
Kroeker et al.[47] (ESRD)	Short daily HD vs conventional HD (3×/wk) in prevalent HD pts	18 mo	Insurer, Canada	73 700
Tonelli et al.[48] (ESRD)	Use of EPO to achieve haemoglobin target of 11–12 g/dL vs haemoglobin target of 9.5–10.5 g/dL in prevalent HD pts	Unstated	Insurer, US	73 800
de Wit et al.[49] (ESRD)	ESRD tx with home or in-centre HD, PD (CAPD or CCPD), or transplantation vs no ESRD tx in Dutch ESRD pts	5	Societal, Netherlands	78 400
Manns et al.[41] (ESRD)	Synthetic dialyzer vs cellulose dialyzer; cost of intervention and related medical costs only (excludes future costs); in male HD pts aged 60 y	Lifetime	Insurer, Canada	86 300
Quinn et al.[50] (ESRD)	Tx with ASA for HD pts with AF vs no tx in HD pts: base case a male aged 60 y on HD with permanent AF	Lifetime	Insurer, US	88 900
Lee et al.[51] (ESRD)	4×/wk, 3 h per session vs conventional HD regimen (3×/wk, 3.5 h per session) in prevalent dialysis pts	Lifetime	Unstated, US	89 000
Glenngard et al.[44] (ESRD)	EPO + RBCT vs RBCT alone in RRT pts on HD	Lifetime	Provider, Sweden	90 500
Quinn et al.[50] (ESRD)	Tx with warfarin vs no tx in HD pts: base case a male aged 60 y on HD with permanent AF	Lifetime	Insurer, US	95 700
Manns et al.[41] (ESRD)	Synthetic dialyzer vs cellulose dialyzer; cost of intervention and related and unrelated medical costs; in male HD pts aged 60 y	Lifetime	Insurer, Canada	97 700
Jassal et al.[42] (transplant)	Cadaveric renal transplantation with 2-y wait vs continued dialysis in non-diabetic dialysis pts aged 65 y who would have to wait ≥2 y for a cadaveric transplant	Lifetime	Insurer, US	98 500
Lee[45] (ESRD)	Starting dialysis when eGFR drops below 7.5 plus an additional 0.4 mL/min/1.73 m^2 for each 1 point of Charlson morbidity score <10 (moderate delay relative to current practice) vs no dialysis in ESRD pts	Lifetime	Unstated, US	99 300

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Table I. Contd

Study (pt population category)	Description	Time horizon (y)[b]	Perspective, country	CUR
Kroeker et al.[47] (ESRD)	Long nocturnal HD vs conventional HD (3×/wk) in prevalent HD pts	18 mo	Insurer, Canada	104 200
Lee[45] (ESRD)	Starting dialysis when eGFR drops below 7.5 plus an additional 0.1 mL/min/1.73 m^2 for each 1 point of Charlson morbidity score <10 (slight delay relative to current practice) vs no dialysis in ESRD pts	Lifetime	Unstated, US	121 600
Sennfalt et al.[37] (ESRD)	PD as initial modality vs no tx in incident dialysis pts aged ≥21 y	5	Societal, Sweden	124 000
Manns et al.[41] (ESRD)	Synthetic dialyzer vs cellulose dialyzer; including future care costs; in male HD pts aged 60 y	Lifetime	Societal, Canada	125 200
Garside et al.[12] (ESRD)	Cinacalcet plus current standard tx (phosphate binders and vitamin D) vs standard tx only in ESRD pts on dialysis with SHPT	Lifetime	Insurer, US	129 100
Lee et al.[51] (ESRD)	5×/wk, 2.5 h per session vs conventional HD regimen (3×/wk, 3.5 h per session) in prevalent dialysis pts	Lifetime	Unstated, US	133 000
Lee[45] (ESRD)	Current practice (starting dialysis when eGFR drops below 9 mL/min/1.73 m^2) vs no dialysis in ESRD pts	Lifetime	Unstated, US	135 900
Lee et al.[52] (ESRD)	Late dialysis initiation (eGFR < 6 mL/min/1.73 m^2) vs no dialysis, waiting for transplant in prevalent dialysis pts	Lifetime	Unstated, US	141 500
Manns et al.[53] (ESRD)	Sevelamer vs CC/calcium-based phosphate binders in ESRD pts	Lifetime	Insurer, Canada	142 400
Sennfalt et al.[37] (ESRD)	HD as initial modality vs no tx in incident dialysis pts aged ≥21 y	5	Societal, Sweden	148 200
Manns et al.[54] (ESRD)	Sevelamer, assuming a survival advantage (RR = 0.91) over the comparator, vs calcium-based phosphate binders in Canadian dialysis pts aged ≥18 y	Lifetime	Insurer, Canada	150 100
Kontodimopoulos and Niakas[23] (transplant)	PD vs HD in ESRD pts	Lifetime	Insurer, Greece	154 700
Lee et al.[52] (ESRD)	No dialysis, waiting for transplant vs current practice for dialysis (3.5–3.75 h sessions 3×/wk) in prevalent dialysis pts	Lifetime	Unstated, US	160 200
	Early dialysis initiation (eGFR <15 mL/min/1.73 m^2) vs no dialysis, waiting for transplant in prevalent dialysis pts	Lifetime	Unstated, US	165 500
Douzdjian et al.[20] (transplant)	Kidney transplant from a living donor vs no action in pts with type 1 diabetes and ESRD, base case assuming graft failure occurs at y 3	5	Insurer, US	197 800
Lee et al.[52] (ESRD)	Late dialysis initiation (eGFR < 6 mL/min/1.73 m^2) vs current practice for dialysis (3.5–3.75 h sessions 3×/wk) in prevalent dialysis pts	Lifetime	Unstated, US	226 900
Jassal et al.[42] (transplant)	Cadaveric renal transplant with 4-y wait vs continued dialysis in non-diabetic dialysis pts aged 65 y who would have to wait ≥2 y for a cadaveric transplant	Lifetime	Insurer, US	281 300
Lee et al.[52] (ESRD)	Early dialysis initiation (eGFR <15 mL/min/1.73 m^2) vs current practice for dialysis (3.5–3.75 h sessions 3×/wk) in prevalent dialysis pts	Lifetime	Unstated, US	333 700

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Table I. Contd

Study (pt population category)	Description	Time horizon (y)[b]	Perspective, country	CUR
Boulware et al.[17] (CKD)	Annual screening for proteinuria vs current practice (no screening of this population) in pts aged 50 y without hypertension or diabetes (base case)	Unstated	Societal, US	360 600
Tonelli et al.[48] (ESRD)	Use of EPO to achieve haemoglobin target of 12.0–12.5 g/dL vs haemoglobin target of 11.0–12.0 g/dL in prevalent HD pts	Unstated	Insurer, US	818 200
	Use of EPO to achieve haemoglobin target of 14.0 g/dL vs haemoglobin target of 12.0–12.5 g/dL in prevalent HD pts	Unstated	Insurer, Canada/US	1 105 400
Douzdjian et al.[20] (transplant)	Kidney transplant from a cadaver vs kidney transplant from a living donor in pts with type 1 diabetes and ESRD, base case assuming graft failure occurs at y 3	5	Insurer, US	Dominated

a CURs presented in $US, year 2008 values.

b In years, unless otherwise indicated.

ACE-I = ACE inhibitor; **AF** = atrial fibrillation; **ASA** = acetylsalicylic acid (aspirin); **CAPD** = continuous ambulatory peritoneal dialysis; **CC** = calcium carbonate; **CCPD** = continuous cycling peritoneal dialysis; **CKD** = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **EPO** = epoetin alpha; **ESRD** = end-stage renal disease; **HCV** = hepatitis C virus; **HD** = haemodialysis; **HLA-B** = human leukocyte antigen-B; **LC** = lanthanum carbonate; **PD** = peritoneal dialysis; **PL** = placebo; **pt(s)** = patient(s); **RBCT** = red blood cell transfusion; **RR** = relative risk; **RRT** = renal replacement therapy; **SHPT** = secondary hyperparathyroidism; **SS** = serological screening; **tx** = treatment.

Further details on the studies and their results are included in league tables of the CURs (table I) and CERs (table II) obtained in this literature search. Details include author, a brief description of the intervention and comparator, time horizon and CUR/CER in $US, year 2008 values. Table III presents a league table of 42 other economic measures of interventions in CKD with results reported in terms other than cost per LY or cost per QALY, such as cost savings per person-year or cost per death prevented. The majority of studies reporting other cost analyses found that the intervention in question was cost saving.

In the following sections, we highlight findings from studies that identified cost-saving interventions as well as other publications showing that the interventions of interest provide reasonable value for money (e.g. CERs under $US100 000 per LY or QALY).

2. Stage 1–4 Chronic Kidney Disease Interventions

Several pharmacological and non-pharmacological interventions are reported to be cost effective or dominant among patients with stage 1–4 CKD. Drug therapies reported in individual studies to be dominant in this population generally reflected benefits associated with slowing the progression of kidney disease and include addition of benazepril (vs no benazepril) to standard antihypertensive therapy in a European population with stage 3 proteinuric kidney disease (the AIPRI [Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency] study);[22] initiation of irbesartan when microalbuminuria develops (vs initiation when overt nephropathy develops) in individuals with type 2 diabetes and hypertension;[57] addition of irbesartan (vs standard care, placebo or amlodipine);[61,62] and the early initiation of irbesartan (vs late addition) among individuals with type 2 diabetes, hypertension and overt diabetic nephropathy.[60] In the RENAAL (Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan) study economic evaluation, treatment with losartan in patients with type 2 diabetes and ne-

Table II. League table of cost-effectiveness ratios (CERs [incremental cost per life-year])[a] in kidney disease

Study (pt population category)	Description	Time horizon (y[b])	Perspective, country	CER
Carides et al.[55] (CKD)	Losartan plus conventional therapy vs conventional therapy in pts with type 2 diabetes, hypertension and nephropathy	Lifetime	Provider, US	Dominant
Costa-Scharplatz et al.[56] (CKD)	Pharmacogenetic testing for the ACE I/D polymorphism before initiating ACE-I therapy, and selective tx vs no testing, non-selective tx in non-diabetic pts with nephropathy and severe persistent proteinuria	3	Insurer, Switzerland	Dominant
Coyle et al.[57] (CKD)	Early addition of irbesartan vs late addition of irbesartan in pts with kidney disease, hypertension and type 2 diabetes	25	Insurer, Canada	Dominant
	Early addition of irbesartan vs conventional care without ARBs in pts with kidney disease, hypertension and type 2 diabetes	25	Insurer, Canada	Dominant
	Late addition of irbesartan vs conventional care without ARBs in pts with kidney disease, hypertension and type 2 diabetes	25	Insurer, Canada	Dominant
Littlewood et al.[58] (CKD)	Standard care with moxonidine vs adjunctive nitrendipine in kidney disease pts (non-ESRD) with hypertension	3	Insurer, Netherlands	Dominant
McLaughlin et al.[59] (ESRD)	Early referral to a multidisciplinary clinic (when creatinine clearance is 20 mL/min) vs late referral to a multidisciplinary clinic (uraemic, requiring RRT) in pts with progressive kidney disease	5	Provider, US/Canada	Dominant
Palmer et al.[60] (CKD)	Early addition of irbesartan vs standard antihypertensive therapy in pts with type 2 diabetes, hypertension and microalbuminuria	25	Insurer, US	Dominant
	Early addition of irbesartan vs late addition of irbesartan in pts with type 2 diabetes, hypertension and microalbuminuria	25	Insurer, US	Dominant
Palmer et al.[61] (CKD)	Irbesartan and standard antihypertensive therapy vs standard antihypertensive therapy in pts with type 2 diabetes, hypertension and microalbuminuria	Lifetime	Insurer, Hungary	Dominant
Rodby et al.[62] (CKD)	Irbesartan vs placebo in pts aged 30–70 y with type 2 diabetes, hypertension and nephropathy	25	Provider, US	Dominant
	Irbesartan vs amlodipine in pts aged 30–70 y with type 2 diabetes, hypertension and nephropathy	25	Provider, US	Dominant
Rosen et al.[35] (CKD)	Medicare first-dollar coverage of ACE-Is vs current practice in all Medicare beneficiaries with diabetes, aged ≥65 y, half with kidney disease; societal perspective	Lifetime	Societal, US	Dominant
	Medicare first-dollar coverage of ACE-Is vs current practice in all Medicare beneficiaries with diabetes, aged ≥65 y, half with kidney disease; Medicare perspective	Lifetime	Medicare, US	Dominant
Sennfalt et al.[37] (ESRD)	PD as initial modality vs HD as initial modality in incident dialysis pts aged ≥21 y	5	Societal, Sweden	Dominant

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Table II. Contd

Study (pt population category)	Description	Time horizon (y[b])	Perspective, country	CER
Huybrechts et al.[63] (ESRD)	Sevelamer (non-calcium-based phosphate binder) vs calcium acetate (calcium-based phosphate binder) in HD pts with mineral abnormalities	1	Insurer, US	2829
Brennan et al.[46] (ESRD)	8-wk trial of LC, if successful continue LC tx, otherwise switch back to tx with CC only vs CC for all in ESRD pts with hyperphosphataemia not adequately maintained on CC	Lifetime	Insurer, UK	30915
Schon et al.[64] (ESRD)	Increase initial access by AVF to 66% of the incident population vs non-AVF initial access (AVG or permanent catheter) in incident dialysis pts	Lifetime	Medicare, US	49023
Manns et al.[41] (ESRD)	Synthetic dialyzer vs cellulose dialyzer; cost of intervention and related medical costs only (excludes future costs); in male HD pts aged 60 y	Lifetime	Insurer, Canada	59054
	Synthetic dialyzer (including future care costs) vs cellulose dialyzer (including future care costs) in male HD pts aged 60 y	Lifetime	Insurer, Canada	85663

a CERs presented in $US, year 2008 values.

b In years, unless otherwise indicated.

ACE-Is = ACE inhibitors; **ARBs** = angiotensin receptor blockers; **AVF** = arteriovenous fistula; **AVG** = arteriovenous graft; **CC** = calcium carbonate; **CKD** = chronic kidney disease; **ESRD** = end-stage renal disease; **HD** = haemodialysis; **I/D** = insertion/deletion; **LC** = lanthanum carbonate; **PD** = peritoneal dialysis; **pt(s)** = patient(s); **RRT** = renal replacement therapy; **tx** = treatment.

phropathy reduced the incidence of ESRD while resulting in substantial cost savings.[74,81]

For patients with diabetes in the US, first-dollar coverage of ACE inhibitors by Medicare was dominant over the current practice of co-payments and/or co-insurance[35] while, in Canada, a programme to pay for ACE inhibitor therapy for patients with type 1 diabetes with nephropathy was reported to be dominant over no programme.[18] Among patients with nondiabetic proteinuric chronic nephropathies, treatment with ramipril has been reported to result in decreased and delayed progression to ESRD, increased survival and cost savings of up to $US5600 per patient per year over conservative treatment (no ACE inhibitor).[73]

Several non-pharmacological interventions among stage 1–4 CKD patients have been reported to be dominant, including early (vs late) referral to a multidisciplinary clinic;[59] pharmacogenetic testing for the ACE insertion/deletion (I/D) polymorphism before initiating ACE inhibitor therapy among non-diabetic patients with nephropathy when compared with non-testing and non-selective therapy;[56] and annual screening for proteinuria for adults aged >50 years with diabetes (vs no screening).[17]

3. Transplantation

The ideal kidney replacement therapy is generally considered to be a kidney transplant, and a number of studies have examined the cost effectiveness of transplantation. In most analyses, kidney transplantation was dominant over both haemodialysis and peritoneal dialysis (PD).[19,20,23,25,31,34,39,66] In a model evaluating interventions for transplant-eligible patients with type 1 diabetes, both cadaveric and living-donor kidney transplants were dominant over continued dialysis.[20] In addition, a number of studies have examined costs related to various pre- and post-transplant clinical strategies. For example, lifetime coverage of immunosuppressive medications by Medicare would extend patient survival by approximately 3 years and would save Medicare approximately $US12 800 over a transplant patient's lifetime, compared with the current policy of 3 years of

Table III. League table of other cost analyses

Study (pt population category)	Description	Time horizon (y[a])	Perspective, country	Estimated costs[b]
Per pt per year costs				
Lefebvre et al.[65] (CKD)	Use of EPO pre-dialysis vs no EPO administration in elderly (aged ≥65 y) CKD pts	1	Provider, US	–66 700
Loubeau et al.[66] (transplant)	Kidney transplant vs HD in renal transplantation pts eligible for Medicare solely due to ESRD	2	Medicare, US	–63 672
Schnitzler et al.[67] (transplant)	Thymoglobulin vs antithymocyte globulin in kidney transplant recipients being treated for biopsy-proven acute cellular rejection	90 d	Societal/Medicare/ transplant centre, US	–35 216
Lee et al.[68] (ESRD)	Total cost of in-centre HD vs PD in ESRD pts	1	Insurer, Canada	–33 913
Shih et al.[69] (ESRD)	PD as initial modality vs HD as initial modality in incident dialysis pts	3	Medicare, US	–23 199
Mohr et al.[70] (ESRD)	Short daily or nocturnal HD vs 3× wkly conventional in-centre HD in adult ESRD pts	1	Societal, US	–16 540
McFarlane et al.[71] (ESRD)	Home nocturnal HD vs in-centre HD in ESRD pts with a life expectancy of ≥1 y	1	Provider, Canada	–11 800
Emparan et al.[72] (transplant)	Basiliximab induction with ciclosporin introduced when creatinine <3 mg/dL vs standard tacrolimus therapy with mycophenolate mofetil in prospective kidney transplant pts to receive immunosuppressant therapy	1	Unstated, Spain	–11 666
Emparan et al.[72] (transplant)	Basiliximab induction with ciclosporin and mycophenolate mofetil (from start) vs standard tacrolimus therapy with mycophenolate mofetil in prospective kidney transplant pts to receive immunosuppressant therapy	1	Unstated, Spain	–7952
Ruggenenti et al.[73] (CKD)	Ramipril vs conservative tx (no ACE-I) in pts with nondiabetic proteinuric CKD	Lifetime	Insurer, Italy	–5611
Herman et al.[74] (CKD)	Losartan plus conventional hypertensive therapy vs PL plus conventional hypertensive therapy in pts with type 2 diabetes, hypertension and nephropathy in the RENAAL study	3.5	Insurer, US	–4702
Lee et al.[68] (ESRD)	Total cost of initial access with a fistula vs graft in ESRD pts	1	Insurer, Canada	–4 106
Plantinga et al.[75] (ESRD)	Attainment of five clinical performance targets: albumin (≥4.0 g/dL), haemoglobin (≥11 g/dL), calcium-phosphate product (<55 mg^2/dL^2), dialysis dose (Kt/V≥1.2), vascular access type (fistula) vs no attainment of clinical targets in HD pts at US non-profit dialysis clinics	1	Societal, US	–3249
Manns et al.[76] (ESRD)	Initial modality AVF vs initial modality AVG in incident HD pts	1	Insurer, Canada	–3001
Lee et al.[68] (ESRD)	Total cost of initial access with a fistula vs catheter in ESRD pts	1	Insurer, Canada	–2 495
Brophy et al.[77] (CKD)	CC plus atorvastatin vs sevelamer in CKD pts with moderate hyperphosphataemia and borderline high-risk LDL cholesterol levels	Unstated	Insurer, US	–2455

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Table III. Contd

Study (pt population category)	Description	Time horizon (y[a])	Perspective, country	Estimated costs[b]
Besarab et al.[78] (ESRD)	SC EPO administration vs IV EPO administration in prevalent HD pts	1	Insurer, US	–2225
Hardinger et al.[79] (transplant)	2-hr post-dose ciclosporin level (C2) monitoring vs trough ciclosporin level (C0) monitoring in kidney transplant recipients	6 mo	Unstated, US	–2030
Taal and van Zyl-Smit[80] (ESRD)	HBV vaccination programme vs standard vaccination programme with frequent antibody screening in HBsAg-negative HD pts who tested negative for anti-HBs and anti-HBc IgG	1	Unstated, South Africa	–1190
Alexander et al.[81] (CKD)	Losartan plus conventional hypertensive therapy vs PL plus conventional hypertensive therapy in pts with type 2 diabetes, hypertension and nephropathy in the RENAAL study	3.5	Unstated, US	–1181
Soroka et al.[82] (ESRD)	HD in renal satellite units vs HD in main renal units in pts with progressive CKD	1	Societal, Canada	–1114
Saab et al.[83] (ESRD)	No screening for immunity, all pts receive vaccination for HBV vs screen for HBV immunity (current practice) in HD pts	5	Unstated, US	–1106
Dominguez et al.[84] (transplant)	2-hr post-dose ciclosporin level (C2) monitoring vs trough ciclosporin level (C0) or 3-hr post-dose ciclosporin (C3) level monitoring in kidney transplant pts	6 mo	Unstated, Chile	–878
Yen et al.[85] (transplant)	Extension to lifetime (20 y) Medicare immunosuppressive coverage vs coverage of only first 3 y following kidney transplantation	1	Societal/Medicare, US	–642
Chuang et al.[86] (ESRD)	HD multiple use (dialyzer sterilized and used again) vs HD single use (dialyzer used only once) in HD pts	1	Unstated, Taiwan	–608
Churchill et al.[87] (ESRD)	Serum ferritin and TSAT laboratory testing decreased to once every 3 mo (minimum recommendation by KDOQI) vs current practice of monthly testing in prevalent dialysis pts	1	Provider, Canada	–631
Churchill et al.[87] (ESRD)	Decrease the frequency of darbepoetin alpha dosing from 2 or 3 doses per wk to 1, or from 1 dose per wk to 1 every other wk vs current practice in prevalent dialysis pts	1	Provider, Canada	–185
Orme et al.[88] (transplant)	Ciclosporin-ME (immunosuppressant) vs tacrolimus in renal transplant recipients	10	Provider, UK	–141
Roderick et al.[89] (ESRD)	HD in renal satellite units vs HD in main renal units in pts with progressive renal insufficiency	1	Unstated, England/Wales	–99
White et al.[90] (ESRD)	Adopting KDOQI guidelines for bone metabolism, specifically guidelines for switching treatment from Ca-based salts to sevelamer vs no adoption of guidelines in HD pts	1	Unstated, Canada	2765
Dykstra et al.[91] (ESRD)	CMS managed care demonstration cohort vs costs if enrolled in an FFS system in adult chronic renal failure pts	1	Medicare, US	4507

Continued next page

Table III. Contd

Study (pt population category)	Description	Time horizon (y[a])	Perspective, country	Estimated costs[b]
Tonelli et al.[92] (ESRD)	Screening AVF access blood flow threshold for angiography at <500 mL/min vs no access screening in prevalent dialysis pts	5	Insurer, Canada	7332
	Screening AVF access blood flow threshold for angiography at <750 mL/min vs no access screening in prevalent dialysis pts	5	Insurer, Canada	6918
Chang et al.[93] (transplant)	Transplant care intervention programme (included pt teaching, help pt return to work and improve social support) vs standard care in non-diabetic kidney transplant recipients	1	Unstated, US	14 235
Population costs				
Lacson et al.[94] (ESRD)	An hypothetical nutritional intervention to improve serum albumin by +0.2 g/dL in 50% of target pts vs standard care in dialysis pts with severe malnutrition (defined as serum albumin ≤3.5 g/dL)	Unstated	Unstated, US	–44 million (projected to entire US ESRD population)
Trivedi et al.[95] (CKD)	Rate of decline in GFR decreased by 10%, 20% or 30% between 1999 and 2010 vs no change in rate of GFR decline in pts with progressive renal insufficiency	10	Societal, US	–27.9, –58.7 and –91.1 billion for 10%, 20% and 30% decreases, respectively, for US ESRD population
Hynes et al.[96] (ESRD)	SC EPO administration with a 32% reduction in dose in 25–75% of pts vs IV EPO administration in prevalent HD pts	1	Medicare, US	–71 to –214 million per y for Medicare
Gerth et al.[97] (ESRD)	Losartan vs conventional hypertensive therapy in ESRD pts with type 2 diabetes and proteinuria	3.5 and 4	Insurer, EU	–4 billion in 3.5 y and –5.6 billion in 4 y for European ESRD population
Other outcome measures				
Ortega et al.[98] (ESRD)	Initial access AVF in incident dialysis pts	1	Societal, Canada	Cost per death prevented: 4653
	Initial access catheter, switch to AVF in incident dialysis pts	1	Societal, Canada	Cost per death prevented: 11 192
	Initial access catheter, no switch in incident dialysis pts	1	Societal, Canada	Cost per death prevented: 13 280
Narayan et al.[99] (ESRD)	Cinacalcet hydrochloride vs parathyroidectomy in ESRD pts with uncontrolled hyperparathyroidism	2	Medicare/Societal, US	The break-even time at which parathyroidectomy became more cost effective than cinacalcet was 7.25 mo

a In years, unless otherwise indicated.

b All costs presented as $US, year 2008 values.

ACE-Is = ACE inhibitors; **anti-HBs** = antibodies to HBsAg; **AVF** = arteriovenous fistula; **AVG** = arteriovenous graft; **Ca** = calcium; **CC** = calcium carbonate; **CKD** = chronic kidney disease; **CMS** = Centers for Medicare and Medicaid Services; **EPO** = epoetin alpha; **ESRD** = end-stage renal disease; **FFS** = fee for service; **GFR** = glomerular filtration rate; **HBc** = hepatitis B core antigen; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HD** = haemodialysis; **IgG** = immunoglobulin G; **IV** = intravenous; **KDOQI** = Kidney Disease Outcomes Quality Initiative; **LDL** = low-density lipoprotein; **ME** = microemulsion; **PD** = peritoneal dialysis; **PL** = placebo; **pt(s)** = patient(s); **TSAT** = transferrin saturation; **SC** = subcutaneous; **tx** = treatment.

coverage.[85] Multiple bills have been introduced in Congress since 2000 to lift the 36-month limit and extend coverage of immunosuppressant drugs indefinitely, and the current health reform legislation proposed in Congress in 2010 also includes a provision for lifetime coverage.[100]

4. End-Stage Renal Disease

Once patients with kidney disease have progressed to ESRD and dialysis, modality choice (haemodialysis vs PD), site of dialysis (home vs in-centre), dialysis frequency and vascular access are all important factors for clinical outcomes and costs; however, the literature is somewhat inconsistent on cost effectiveness. For example, in Swedish patients, PD was reported to be the dominant strategy compared with haemodialysis over a 5-year timeframe[37] while conversely, in a study of Greek patients (with a lifetime perspective), PD was found to be a more costly strategy than haemodialysis.[23] Another cost analysis comparing PD with haemodialysis (which found no difference in mortality across interventions) noted that PD cost $US23 200 less per patient per year.[69]

Compared with conventional haemodialysis, daily haemodialysis has been reported to decrease the number of hospital days by 43%, decrease the average weekly dose of erythropoiesis-stimulating agents (ESAs) by 41%, and decrease the average number of antihypertensive medications by 47%, with total patient cost savings ranging from $US11 800 to $US16 500 per patient per year.[70,71] Another study found that the incremental cost per QALY of short daily haemodialysis and long nocturnal haemodialysis versus conventional haemodialysis were $US73 700 and $US104 200, respectively.[47] Similarly, compared with a conventional haemodialysis regimen of three times per week at 3.5 hours per session, the incremental cost per QALY of a haemodialysis regimen of four times per week at 3 hours per session was $US89 000 and that of a regimen of five sessions per week at 2.5 hours per session was $US133 000.[51]

Among haemodialysis patients, the economic evidence suggests that access with a functioning native arteriovenous fistula (AVF) costs less than access with either a catheter or graft.[68,76] On a population basis, the incremental cost effectiveness of increasing the rate of initial access with AVFs from 35% to 66% has been estimated at $US49 000 per LY gained.[64]

5. Complications and Co-Morbidities

Care of individuals receiving dialysis has been the subject of numerous clinical practice guidelines, and studies of the costs and cost effectiveness of implementing guidelines have produced equivocal results.[90] In one cohort study examining the cost effectiveness of achieving the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) targets,[75] hospitalization costs decreased when any of the five clinical targets were attained; however, only the achievement of a targeted value for albumin resulted in statistically significant cost savings ($p = 0.002$). Attainment of multiple targets decreased hospitalization costs ($p = 0.05$ for attainment of all five targets). While, in this cohort study and others, attainment of increasing numbers of targets was significantly associated with decreased mortality, fewer hospitalizations and fewer hospital days,[75,101,102] no randomized trial has demonstrated an improvement in clinical outcomes associated with interventions designed to facilitate achievement of these targets. In some instances, achieving a certain guideline or target has not resulted in improved clinical outcomes; for example, lower blood pressure levels that are consistent with achieving the KDOQI target have, in one study, been associated with increased mortality.[103]

Anaemia is a common co-morbidity among dialysis patients, and ESAs are commonly used for treatment. Several studies have examined the cost effectiveness of various ESA treatments, including epoetin alfa (EPO). One meta-analysis suggested that, if EPO administration were subcutaneous rather than intravenous, drug-related cost savings may be attainable because of a reduction in EPO dose, although neither the potential for increased costs related to more frequent transfusions nor the issue of differential pain of subcutaneous versus intravenous injections were

considered.[78] Other studies have suggested that the intravenous and subcutaneous methods can result in similar doses administered over a longer follow-up period, particularly in patients with adequate iron stores.[104,105]

As the primary cause of death in haemodialysis patients is cardiovascular disease (CVD), the management of cardiovascular co-morbidities is frequently discussed as a potential area for improvements in care that might lead to cost savings.[106,107] Unfortunately, very few cost-effectiveness studies have been published of intervention strategies in the kidney disease population with CVD. Data gaps exist because people with kidney disease are often excluded from clinical trials, and results of other trials cannot necessarily be extrapolated to the kidney disease population.[108] Paradoxically, based on one analysis, some risk factors for CVD in the general population – such as body mass index (BMI), hypercholesterolaemia and hyperlipidaemia – have been reported to be correlated with better survival in haemodialysis patients.[109] In turn, certain established treatments for CVD in the general population have not been successful in people with ESRD; for example, both the German 4D (Diabetes and Dialysis) study of atorvastatin in 1255 high-risk haemodialysis patients with diabetes and elevated cholesterol, as well as the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) study of rosuvastatin in 2776 haemodialysis patients aged 50–80 years, failed to show a benefit despite successful lowering of low-density lipoprotein (LDL) cholesterol in both studies.[110,111]

6. Vaccination and Other Preventive Care

Hepatitis B virus (HBV) vaccination is common among patients with advancing kidney disease and ESRD because it is required by dialysis clinics to prevent spread to other patients and to staff.[112] It has been reported that HBV vaccination among incident dialysis patients in a region where HBV is endemic saves about $US1200 per patient in the first year and about $US5000 per patient in subsequent years.[80] Current practice is to screen patients for HBV immunity rather than giving all haemodialysis patients annual HBV vaccine boosters without screening. However, despite this practice, one cost analysis reported that routine annual vaccination of all patients on haemodialysis, with no serological screening, saves about $US1100 per patient per year (with fewer patients in the screening cohort having hepatitis B infections).[83]

Researchers have suggested that more thorough preventive care (e.g. diabetic care, influenza vaccination and lipid monitoring) for the kidney disease population could potentially save money because better care management overall could result in fewer preventable hospitalizations and other types of resource utilization.[112] Similarly, research suggests that increasing the proportion of patients with diabetes who receive regular foot[113] and eye screening[114] and glycosylated haemoglobin (HbA_{1c}) testing may be cost effective.[115] No cost-effectiveness data are available specifically for the diabetic kidney disease population, but there is some evidence that educational and prevention programmes focused on diabetic self-care in the dialysis setting may decrease the number of costly amputations.[116]

7. Discussion

The current review surveys and summarizes the recent economic literature concerning interventions in patients with stage 1–4 CKD and ESRD, including kidney transplantation, focusing on studies that reported incremental CURs (cost per QALY) and CERs (cost per LY). There is evidence that there may be opportunities to lower costs in the treatment of CKD patients and improve or at least maintain the quality of care. In order to realize these cost savings, efforts will be required to promote and effectively implement changes in treatment practices. However, interventions that appear to be cost effective should be subject to additional in-depth research. For example, comparative effectiveness studies of cost-effective interventions in real-world settings may be warranted, in order to support translation of research into practice.

Variations existed both within and across intervention types. For example, there is no consensus regarding the optimal initial dialysis modality. Most of the discrepancies in estimates may be explained by differences in CEA methodologies, as a number of issues can have a major impact on the result of a CEA, including the perspective taken, discounting used, time horizon, target population characteristics (such as age and co-morbidities), and whether or not the survival benefits are quality adjusted.

Our findings add to the already considerable body of literature outlining a need for improved care as well as the potential consequences to the US healthcare system if the costs of treating CKD are not lowered. Given the high cost of caring for the existing ESRD population and the alarming epidemiological predictions of future growth of the ESRD population,[3] we need a better understanding of the cost effectiveness of clinically beneficial interventions.

7.1 Policy Implications

This study identified a substantial number of interventions for the CKD population that appeared to be either cost effective or cost saving. However, two key questions need to be carefully considered to fully understand the implications of this study: (i) for interventions that are not widely used, how feasible is it to facilitate adoption? (ii) how might US payment reform affect the likelihood of adopting cost-saving interventions?

7.1.1 Difficulties in Adopting Interventions

Although transplantation is the optimal treatment for kidney failure in the majority of patients, from both a clinical and an economic standpoint, increasing transplantation rates would be difficult to achieve without implementing sweeping policy changes and/or changes in societal attitudes toward organ donation. The same may hold true for changes in the use of alternative dialysis modalities (such as PD or home haemodialysis vs in-centre haemodialysis), which would likely require both a realignment of incentives – perhaps with better reimbursement for patient education – as well as more clinical training for practitioners in these modalities.

Alternatively, the most recent data suggest that approximately 80% of patients with stage 3–4 CKD in the US have hypertension, but only 20% are adequately managed.[3] In our review, a number of different studies of various antihypertensive medications found that they were dominant over conventional therapy or that the earlier use of these medications was dominant over later use. In order to realize more cost savings via antihypertensive therapies and other medical interventions, modifications in treatment patterns would likely be required. The mechanisms used to try to reform clinical practice patterns in the past for patients with kidney disease, such as clinical practice guidelines, have experienced limited success.[117] Moreover, clinicians cannot alter outcomes on their own but must do so in partnership with patients. Nevertheless, medication management programmes and value-based benefit design (e.g. waiving co-payments on long-term medications) are possible ways to facilitate greater use of antihypertensive medications among patients with kidney disease.

7.1.2 Payment System Surrounding Care for Kidney Disease Patients

There are a number of important changes taking place in the arena of reimbursement and policy in the US that could affect whether cost-effective interventions are used in the kidney disease population. First, policy makers have recently attempted to address the need for better education in the Medicare Improvements for Patients and Providers Act of 2008 (MIPPA), which provides Medicare reimbursement for education services for patients with stage 4 CKD.[118]

Additionally, MIPPA mandated a major change in dialysis reimbursement, with the current payment bundle expanding in 2011 to include most injectable medications and their oral equivalents administered for dialysis care.[119] Most notable among these are the ESAs, the dose of which depends on multiple factors, including overall patient health. This new reimbursement policy represents a shift in risk distribution away from the Centers for Medicare and Medicaid Services (CMS) and toward the dialysis providers, providing greater financial incentives for dialysis units to provide less expensive care. Whether this

could lead to 'cherry-picking' healthier, better insured or more compliant patients under the new payment system or empower dialysis providers to influence pre-dialysis care through dissemination of cost-effective interventions such as earlier patient education, including emphasis on fistula creation and modality choice, remains uncertain.[120]

Additional reimbursement for such coordination, including introduction of 'medical homes' in nephrology, could enable providers to look for ways to improve care beyond the dialysis setting and into primary care and management of comorbidities, although it clearly would require a substantial reconceptualization of care for ESRD patients. Furthermore, the requirements of serving as a medical home may be unattainable for some nephrologists, particularly those in smaller practices.[121] Critically, this expanded bundling of payment makes comparative effectiveness research with subsequent cost comparisons essential to aid dialysis providers in making the best choices within limited financial resources, and to aid CMS and other payers in implementing policies designed to achieve the greatest health benefits for patients. Finally, general US health reform, which was recently implemented, could have a positive impact on earlier stage CKD patients, by improving insurance coverage and access to therapies that could slow the progression to ESRD.

7.2 Limitations

This review is limited in several ways. First, our review was limited to the current published literature, meaning that interventions that have not yet been the subject of a cost analysis could not be included in our results. One example is the area of vaccination – while data exist for HBV, the economic impact of influenza or pneumococcal pneumonia vaccination for the CKD population is not available. Second, our conclusions are limited by the quality of the underlying evidence (which is varied in terms of its source, relevance and strength) as well as variability in the methods used to determine cost effectiveness. All of the CEAs discussed in this review are based on assumptions about the clinical effectiveness of the intervention under investigation. Some of the studies may be outdated and no longer relevant to current practice, and, for older studies, updating original estimates to current dollars can have a large effect on ratios originally reported. Furthermore, we did not evaluate the quality of the underlying studies that led to effectiveness assumptions. In particular, with the exception of economic evaluations of antihypertensive therapies, which used data from randomized controlled trials, most of the clinical evidence underlying the CEAs was based on observational studies. Publication bias may also play a role in overestimating the effectiveness and/or underestimating the costs in CEAs,[122,123] and may also affect the overall quality of a CEA.[124,125] It was beyond the scope of this article to provide an assessment of the quality of the articles included in the literature review, and we also acknowledge that funding source could have impacted the results of the studies included in our review.

Finally, it should be noted that cost effectiveness and QALYs are not yet widely used or endorsed in US health policy decision making.[126] Neither the US FDA nor Medicare requires manufacturers to provide cost-effectiveness data to inform regulatory and reimbursement decisions. The most recent proposals for US Government-sponsored comparative effectiveness research also lack any imperative to consider economic data.[127] Research suggests that US policy makers have doubts about the methodological soundness of the cost-effectiveness approach,[126] although a recent review has indicated that cost-effectiveness methodologies have improved.[128] Nonetheless, there is a strong interest in understanding the cost effectiveness of healthcare interventions globally, as shown by the rapidly expanding literature.[129]

8. Conclusion

This comprehensive review of the recent economic literature found evidence that opportunities exist to improve outcomes and provide value for money in the treatment of CKD and ESRD. More information is needed concerning some of the treatment approaches that have been reported to reduce costs but have not yet been studied from

an incremental cost per QALY perspective. In addition, some of the interventions that have been reported to be cost saving may be difficult to put into practice, requiring systematic implementation approaches and coordinated efforts from many players. Nevertheless, this review provides valuable information on the scope of cost effectiveness in CKD and ESRD that will be of interest to policy makers, researchers and clinicians, especially in light of changes in the reimbursement for dialysis services in the US and US health reform more generally.

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