ECONOMIC MODELLING OF CHRONIC KIDNEY DISEASE: A SYSTEMATIC LITERATURE REVIEW TO INFORM CONCEPTUAL MODEL DESIGN

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Supplementary Table 8. Summary of unique models: Model setting

Study	Year	Country	Perspective	Time horizon	Type of analysis	Model type	Disease setting	Research question
Boersma et al[1]	2010	Netherlands	Healthcare	8 years	Cost-effectiveness and budget impact	Markov model	General population	Estimate the cost-effectiveness and budget impact of various population-based screen-and-treat scenarios for elevated albuminuria levels (i.e. microalbuminuria)
Boulware et al[2]	2003	USA	Societal	NR	Cost-effectiveness	Markov decision analytic model	US patients with neither hypertension nor diabetes and adults with hypertension	Assess the value (QALY) of periodic, population-based dipstick screening for early detection of urine protein in adults with neither hypertension nor diabetes and in adults with hypertension
Elbasha et al[3]	2017	USA	Third party payer	NR	Cost-effectiveness	Semi-Markov model	Hepatitis C virus genotype 1 infection and CKD	Cost-effectiveness of elbasvir/grazoprevir in treatment-naïve and treatment-experienced CKD patients compared with no treatment and pegylated interferon plus ribavirin using a computer-based model of the natural history of chronic hepatitis C virus genotype 1 infection, CKD and liver disease
Erickson et al[4]	2013	USA	Societal	Lifetime	Cost-effectiveness	Markov model	CKD and hypertension	Cost-effectiveness of statins for primary prevention of myocardial infarction and stroke in patients with CKD
Ferguson et al[5]	2017	Canada	Health payer	45 years or until death	Cost-utility	Markov model	Canadian indigenous	Assess the cost utility of screening and subsequent treatment for CKD in rural Canadian indigenous adults by both eGFR and the urine albumin-to-creatinine ratio
Hoerger et al[6]	2010	USA	Healthcare	Age 50 to 90 years or death	Cost-effectiveness	Discrete microsimulation model	US patients	Cost-effectiveness of screening for microalbuminuria followed by treatment with angiotensin converting enzyme inhibitors or angiotensin II-receptor blockers for African Americans and non-African Americans
Howard et al[7]	2010	Australia	Healthcare	Lifetime	Cost-effectiveness	Markov model	Patients with risk factors (diabetes, hypertension and proteinuria)	Assessed, from the perspective of a health-care funder, the health outcomes (measured in terms of QALYs) and incremental costs of intensive management of patients known to have diabetes and hypertension, with and without early detection of new patients at risk for CKD, compared with current practice
Levy et al[8]	2014	USA	NR	30 years	Cost-effectiveness	Markov model	CKD	Predict the timing and number of cases of end-stage renal disease, survival and QALYs occurring over the projected lifetime of a cohort of hypothetical CKD patients based on a range of baseline eGFR values and of rates of eGFR decline
Nuijten et al[9]	2010	UK	NHS (separate analysis performed from societal	10 years	Cost-effectiveness	Markov model	CKD with secondary hyperparathyroidism	Assess the cost effectiveness of paricalcitol for secondary hyperparathyroidism in CKD compared with alfacalcidol

			perspective)					
Nuijten et al[10]	2009	USA	Third party payer	11 years	Cost-effectiveness	Markov model	CKD with secondary hyperparathyroidism	Cost-effectiveness of paricalcitol versus calcitriol for the treatment of secondary hyperparathyroidism in patients with CKD
Okubo et al[11]	2015	Japan	Societal	Lifetime	Cost-effectiveness	Decision tree and Markov model	CKD or diabetes	Cost-effectiveness of obstructive sleep apnea screening for patients with diabetes or CKD
Orlando et al[12]	2011	USA	NR	Lifetime	NR	Markov model	CKD	Evaluate the impact of 7 different treatment strategies on outcomes including QALYs, mortality, cardiovascular disease, disease progression, and bone disease
Schlackow et al[13]	2017	UK	NR	5 years	Cost-effectiveness	Markov model	CKD and cardiovascular disease	Long-term policy model of cardiovascular disease in moderate-to-advanced CKD

ACEI: angiotensin converting enzyme inhibitor; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; NA: not applicable; NHS: National Health System; NR: not reported; QALY: quality-adjusted life year.

Supplementary Table 9. Summary of unique models: health states, disease progression, CV events and discount rates

Study	Health states related to kidney disease	Approach used to model CKD progression	Approach used to model CV events	Discounting
Boersma et al[1]	Low normo-albuminuria, high normo-albuminuria, microalbuminuria, macro-albuminuria, dialysis, death	Transition probabilities UAE	Probability of MI, derived from Dutch Renal Registry	4% and 1.5%
Boulware et al[2]	Normal kidney function CKD 1, CKD 2-4, CKD 5, death	Annual rate of eGFR decline	NR	3%
Elbasha et al[3]*	CKD 1, CKD 2, CKD 3A, CKD 3B, CKD 4, CKD 5, haemodialysis, kidney transplant	Transition probabilities	Risk of stroke and MI, dependent on CKD stage	NR
Erickson et al[4]	CKD 3a + 3b, CKD 4, ESRD, death	Annual rate of eGFR decline	Probability of MI, stroke, myopathy, partly derived from Framingham risk scores	3%
Ferguson et al[5]	CKD 1a-2b, CKD 3a, CKD 3b, CKD 4, kidney failure, dialysis, surviving with kidney transplant, death	Transition probabilities	NR	5%
Hoerger et al[6]	no CKD, CKD 1, CKD 2, CKD 3, CKD 4, CKD 5, death	Annual GFR decrement and transition rates	Probability of MI, stroke and CAD, derived from Framingham risk scores	3%
Howard et al[7]	Diabetes normoalbuminuria ± hypertension, diabetes microalbuminuria ± hypertension, diabetes macroalbuminuria ± hypertension, hypertension ± proteinuria, Proteinuria, CKD, ESRD requiring RRT, dialysis, transplant, death	Relative risk of progression	Relative risk of CV event of CV death, derived from randomized trials	5%
Levy et al[8]	Functioning kidney: CKD 3a, CKD 3b, CKD 4, CKD 5 Kidney failure: dialysis, transplant Death	Annual eGFR decline Transition probabilities to ESRD	NR	3%
Nuijten et al[9]	CKD 1, CKD 2, CKD 3, CKD 4, CKD 5, transplant, death	Transition probabilities	NR	3.5%
Nuijten et al[10]	CKD 1, CKD 2, CKD 3, CKD 4, CKD 5, transplant, death	Transition probabilities	NR	3.5%
Okubo et al[11]	CKD patients: screened and/or examined CKD ESRD, cardiovascular disease, death Diabetes patients: screened and/or examined diabetes, ESRD, death	Transition probabilities	NR	3%
Orlando et al[12]*	No CKD no risk, No CKD high risk, CKD 1, CKD 2, CKD 3, CKD 4, CKD 5, dialysis, transplant, dead	Monthly GFR changes	Probability of MI (dependent on cardiovascular disease state). Probability of stroke (dependent on CKD stage) Probability of hypertension (dependent on	3%

			CKD stage)	
Schlackow et al[13]	CKD 3B, CKD 4, CKD 5 not on RRT, dialysis, transplant	Risk equations	NR	NR

CKD: chronic kidney disease; CV; cardiovascular; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; KT; kidney transplant; MI: myocardial infarction; NA: not applicable; NR: not reported; RRT: renal replacement therapy; UAE: urinary albumin secretion.

** Studies included additional non-renal health states.*

Supplementary Table 10. Summary of unique models: Sensitivity analyses and drivers of cost effectiveness

Study	Sensitivity analyses	Drivers of cost-effectiveness	Validation
Boersma et al[1]	Probabilistic and one-way	CV morbidity cost estimate, lowering or increasing the costs of pre-screening on urinary albumin concentration, costs for the urinary albumin excretion confirmation test, and costs of angiotensin-converting enzyme inhibitor treatment	NR
Boulware et al[2]	One-way	Age when screening begins, frequency of screening	Compared model output with nationally available data on disease incidence and mortality
Elbasha et al[3]	Deterministic and probabilistic	Changes in discount rates, impact of Hepatitis C virus on CKD progression or death, death from hepatocellular carcinoma and utility following sustained virologic response	Several tests were built into the model for verification and to ensure internal validity e.g. the sum of the distribution of persons in each health state at the end of each cycle was verified to be equal to 1 both numerically
Erickson et al[4]	Probabilistic	The range of rhabdomyolysis risk in CKD, cardiovascular risk, severity of CKD upon initiation, and relative risk reduction in CKD progression	Compared life expectancies produced from each patient group to U.S. life tables, demonstrating stepwise decreases following additions of hypertension, non-progressive CKD, and progressive CKD
Ferguson et al[5]	One-way	Rate of progression to ESRD, prevalence of albuminuria	Compared life tables in Manitoba's indigenous population with the life expectancy determined in the Markov simulation
Hoerger et al[6]	One-way	Micro-albuminuria incidence, treatment adherence, discount rate	Validated the model according to recommended standards outlined by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force
Howard et al[7]	One—way and probabilistic	NR	NR
Levy et al[8]	One-way	Time horizon and to a lesser extent, age at entry; the number per 1,000 reaching ESRD is most sensitive to the HR for eGFR and the time horizon; and the cost per QALY is most sensitive to the HR for ESRD and the daily treatment cost	Model verification included testing for internal consistency using extensive debugging and testing extreme conditions
Nuijten et al[9]	One-way and probabilistic	Variables were input variables related to proteinuria (progression to proteinuria, mortality with proteinuria)	NR
Nuijten et al[10]	One-way and probabilistic	Variables were input variables related to proteinuria (progression to proteinuria, mortality with proteinuria)	Subjected to internal testing and debugging, as well as being calibrated against NHANES data
Okubo et al[11]	One-way	Change of utility weight with CPAP treatment	NR
Orlando et al[12]	One-way	No variables were identified that significantly changed the outcome results when varied across their plausible range	To externally validate the CKD model, the model's cohort was altered to reflect participants of two different published studies, Go (2004) and in Wright (2002, AASK trial), and model's projections were compared.
Schlackow et al[13]	NR	Model-simulated cumulative rates of cardiovascular endpoints (all participants) and progression to RRT (those not on RRT at entry) were internally validated through comparison with the 5-year Kaplan-Meier product-limit estimates in SHARP, across all participants, and in subgroups by CKD status.	SHARP participants were followed for an average of 5 years and hence the longer-term predictions are guided by the model structure and parametric proportional hazards assumptions. SHARP excluded patients with major coronary disease, whereas in routine clinical practice coronary heart disease is highly prevalent in moderate-to-advanced CKD. Future model developments could consider further disease markers and endpoints

CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ESRD: end stage renal disease; HR: hazard ratio; NHANES: National Health and Nutrition Examination Survey; NR: not reported; QALY: quality-adjusted life year; RRT: renal replacement therapy; SHARP: Study of Heart and Renal Protection.

References

1. Boersma C, Gansevoort RT, Pechlivanoglou P, et al. Screen-and-treat strategies for albuminuria to prevent cardiovascular and renal disease: cost-effectiveness of nationwide and targeted interventions based on analysis of cohort data from the Netherlands. Clin Ther. 2010;32(6):1103-21.
2. Boulware LE, Jaar BG, Tarver-Carr ME, et al. Screening for proteinuria in US adults: a cost-effectiveness analysis. Jama. 2003;290(23):3101-14.
3. Elbasha E, Greaves W, Roth D, et al. Cost-effectiveness of elbasvir/grazoprevir use in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and chronic kidney disease in the United States. J Viral Hepat. 2017;24(4):268-79.
4. Erickson KF, Japa S, Owens DK, et al. Cost-effectiveness of statins for primary cardiovascular prevention in chronic kidney disease. J Am Coll Cardiol. 2013;61(12):1250-8.
5. Ferguson TW, Tangri N, Tan Z, et al. Screening for chronic kidney disease in Canadian indigenous peoples is cost-effective. Kidney Int. 2017;92(1):192-200.
6. Hoerger TJ, Wittenborn JS, Segel JE, et al. A health policy model of CKD: 2. The cost-effectiveness of microalbuminuria screening. Am J Kidney Dis. 2010;55(3):463-73.
7. Howard K, White S, Salkeld G, et al. Cost-effectiveness of screening and optimal management for diabetes, hypertension, and chronic kidney disease: a modeled analysis. Value Health. 2010;13(2):196-208.
8. Levy AR, Perkins RM, Johnston KM, et al. An epidemiologic model to project the impact of changes in glomerular filtration rate on quality of life and survival among persons with chronic kidney disease. Int J Nephrol Renovasc Dis. 2014;7:271-80.
9. Nuijten M, Andress DL, Marx SE, et al. Cost Effectiveness of Paricalcitol versus a non-selective vitamin D receptor activator for secondary hyperparathyroidism in the UK: a chronic kidney disease markov model. Clin Drug Investig. 2010;30(8):545-57.
10. Nuijten M, Andress DL, Marx SE, et al. Chronic kidney disease Markov model comparing paricalcitol to calcitriol for secondary hyperparathyroidism: a US perspective. Curr Med Res Opin. 2009;25(5):1221-34.
11. Okubo R, Kondo M, Hoshi SL, et al. Cost-effectiveness of obstructive sleep apnea screening for patients with diabetes or chronic kidney disease. Sleep Breath. 2015;19(3):1081-92.

12. Orlando LA, Belasco EJ, Patel UD, et al. The chronic kidney disease model: a general purpose model of disease progression and treatment. BMC Med Inform Decis Mak. 2011;11:41.

13. Schlackow I, Kent S, Herrington W, et al. A policy model of cardiovascular disease in moderate-to-advanced chronic kidney disease. Heart. 2017.