Comparison of antihypertensive therapies

Adarkwah 2013

Study	Adarkwah CC, Gandjour A, Akkerman M et al. (2013) To treat or not to treat? Cost-effectiveness of ace inhibitors in non-diabetic advanced renal disease: a Dutch perspective. Kidney and Blood Pressure Research 37: 168-180			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost utility analysis **Study design:** Decision analytic model **Approach to analysis:** Markov model[1] simulating the progression of 1000 people through 3 health states: advanced renal disease, ESRD and death. Probabilistic sensitivity analysis used 1,000 Monte Carlo simulations. **Perspective:** Dutch health system **Time horizon:** Until cohort age of 100 (>99% of cohort dead), 1-year cycle with half-cycle correction **Intervention effect duration:** duration of the analysis **Discounting:** 4% costs, 1.5% QALYs	**Population:** People aged 44 with advanced renal disease[2] **Cohort settings** **Intervention 1:** ACE inhibitor **Intervention 2:** No treatment (Antihypertensives not acting on the renin-angiotensin-system[3])	**Total costs (mean per individual)[4]:** **Int 1:** €183, 535 (£176,674) **Int2**: €220,942 (£212,683) **Currency & cost year:** Euros, 2010 **Cost components incorporated:** direct healthcare costs (ACE inhibitor, chronic kidney disease costs, transplant and dialysis)	**QALYs (mean per individual):** **Int1**: 14.66 **Int 2:** 13.38	**Full incremental analysis:** The ACE inhibitor strategy dominates the no treatment strategy having a lower cost and higher benefit. **Analysis of uncertainty:** Parameters with largest impact in univariate sensitivity analysis were the effectiveness of ACE inhibitor, cost of ESRD and discount rate. The conclusions of the analysis did not change when these were varied. The probability of producing savings was 83%.

Data sources
Outcomes: The author conducted a literature review from 2001 to September 2012 to update an existing systematic review on the effect of ACE inhibitors (Terajima 2003). Two RCTs met the inclusion criteria (Ihle 1996 and Hou 2006) and informed the probability of transition to the ESRD state in people receiving ACE inhibitor, and in the no treatment arm (baseline risk). In the advanced renal disease group mortality was modelled using national age specific national rates adjusted for disease specific mortality using cohort data (Hemmelgarn 2010). For people with ESRD mortality was assumed to be age independent. **Quality of life weights:** The utility for people in the advanced renal disease stage was sourced from a survey using TTO (Hoerger 2010). ESRD state preferences were sourced from a publication applying a TTO methodology in 272 people in ESRD (Churchill 1987). **Costs:** The base case used the cost of the cheapest generic of benazepil 10 mg available in the Netherlands. The annual cost of renal transplant and different types of dialysis was sourced from was sourced from a Dutch study (de Wit 1998) and prevalence data from a The Dutch End-Stage Renal Disease registry (2011b). Transplant survival was assumed to be 10 years.
Comments
Source of funding: None. No conflicts of interest.
Overall applicability: Partially applicable
Analysis conducted 6 years ago taking a Dutch health system perspective. The analysis considers only one class of antihypertensive medication in CKD progression. Costs were discounted at a 4% annual rate and benefits at a 1.5% rate. This may have contributed to the cost-effectiveness of the intervention, compared to a scenario were both costs and benefits were subject to 3.5% annual discounting.
Overall quality: Potentially serious complications
The absolute effect of the intervention was assumed constant over the duration of the analysis as was the risk of progressing to ESRD. It is likely that technologies such as dialysis and transplant may have different costs and safety profiles since the analysis was conducted.

[1]Model adapted from previous analysis of the cost effectiveness of ACE inhibitors in Germany (Adarkwah 2010) and the Netherlands (Adarkwah 2011)

[2]Serum creatinine: > 3.0 mg/dl, glomerular filtration rate (GFR): 15-26 ml/min/1.73 m²), proteinuria, and hypertension (> 150/85 mm Hg), but without severe heart failure (New York Heart Association III or IV) or diabetes.

[3]People in the control arm were allowed diuretics, calcium-channel antagonists, alpha- or beta-blockers, or a combination of these, excluding ACE inhibitors and angiotensin II–receptor antagonists.

[4]Euros 2010 converted to sterling 2019 using the EPPI Centre cost converter (accessed 12/12/2019), conversion factor 1.04

Delea 2009

Study	Delea TE, Sofrygin O, Palmer JL et al. (2009) Cost-effectiveness of aliskiren in type 2 diabetes, hypertension, and albuminuria. Journal of the American Society of Nephrology 20: 2205-13			
Study details	**Population & interventions**	**Costs**	**Outcomes**	**Cost effectiveness**

Economic analysis: Cost utility analysis **Study design:** Decision analytic model **Approach to analysis:** Markov model[1] simulating progressive kidney disease using several health states: microalbuminuria, early overt nephropathy, advanced overt nephropathy, doubling serum creatinine, dialysis, transplant and death. Probabilistic sensitivity analysis used 1,000 Monte Carlo simulations. **Perspective:** US health system **Time horizon:** lifetime, 6-month cycles **Intervention effect duration:** lifetime **Discounting:** Cost and QALYs at 3% annually	**Population:** People with type 2 diabetes and microalbuminuria **Cohort settings** **Intervention 1:** Aliskiren 300 mg/day plus losartan 100 mg/day* **Intervention 2:** Losartan 100 mg/day* *Plus optimal antihypertensive therapy	**Total costs (mean per individual)[2]:** **Int1:** $64,746 (£53,849) **Int 2:** $61,794 (£51,394) **Currency & cost year:** US dollars, 2008 **Cost components incorporated:** direct healthcare costs (intervention costs, additional antihypertensive costs,	**QALYs (mean per individual):** **Int1:** 5.9775 **Int2:** 5.8808 **Other:** Incidence of ESRD: **Int1:** 23.43% **Int2:** 20.74% (2.69% reduction, favours intervention 1) Time free of ESRD: Increased by 0.1772 years, favours intervention 1	**Full incremental analysis[3]:** In the base case aliskiren combined with losartan was more expensive and produced more QALYs than the strategy using losartan alone producing an ICER of $30,527/QALY (£25,390/QALY). **Analysis of uncertainty:** In univariate sensitivity analysis the results were sensitive to the duration of effect and price of aliskiren but the intervention remained cost-effective at the $50,000 to $100,000/QALY (£41,585 to £83,170/QALY) threshold. Interventions 1 had a 60% probability of being cost-effective at a $50,000/QALY threshold and a 72% probability of being cost-effective at a threshold of $100,000.

Data sources

Outcomes: In the initial 6 months the distribution of people and probability of transiting between the microalbuminuria, early overt nephropathy and advanced overt nephropathy states was estimated using patient level data from the AVOID trial (Parving 2008). After 6 months the probabilities were estimated using Bayesian conjugate analyses of these data not allowing for backward or double forward transitions. The probability of transiting to the double serum creatinine state and ESRD dialysis was sourced from the cost-effectiveness analysis by Palmer (2004). The probability of transplant and graft failure for those on dialysis was sourced from the US Renal Data System (2007). Mortality on those without ESRD was implemented using US lifetables (WHO 2008) adjusted for diabetic nephropathy specific mortality using a risk ratio (diabetic nephropathy versus general population) from Palmer (2004). Age-specific mortality for those on the ESRD stages was estimated from the US Renal Data System (2007). Adverse events were not modelled as they were similar between arms of the AVOID trial.

Quality of life weights: Health state utilities were calculated by multiplying age-specific utilities in the US population by health state disutilities. The disutilities for early chronic kidney disease and renal transplantation were sourced from cohort studies using TTO to elicit preferences (Fryback 1993 and Kiberd 1995, respectively). The disutility for dialysis was sourced from a study eliciting utility values from 2,048 people with diabetes using a self-administer questionnaire (Coffey 2002).

Costs: The use of aliskiren, losartan and additional antihypertensive medicines was estimated during the AVOID trial (Parving 2008). Unit costs used wholesale drug prices and the IMS National prescription audit (2008). The cost of routine healthcare in people with diabetes used data from a cost-effectiveness analysis of diabetes screening (Centres for Disease Control and Prevention, 1998) and from the Diabetes Control and Complications Trial (1996). Costs of dialysis, renal transplantation and graft failure were obtained from the US Renal Data System (2007).
Comments
Source of funding: The analysis was funded by the drug manufacturers. Several authors have received consulting fees from drugs manufacturers.
Overall applicability: Partially applicable
Conducted 10 years ago from an US health system perspective. The analysis does not compare all medicines available in this decision space. The analysis was sponsored by the drug manufacturer. Aliskiren is not a drug in routine use in the UK.
Overall quality: Potentially serious limitations
Progression in the model is essentially sourced from a single RCTs, adverse events were not modelled because RCT found incidence to be identical in the comparator included in the trial.

[1]Markov model adapted from US cost effectiveness analysis of ACE inhibitors in people with diabetes, hypertension and renal disease (Palmer 2004)

[2]US dollars 2008 converted to sterling 2019 using the EPPI Centre cost converter (accessed 17/12/2019), conversion factor 1.20

Smith 2004

Study	Smith DG, Nguyen AB, Peak CN et al. (2004) Markov modeling analysis of health and economic outcomes of therapy with valsartan versus amlodipine in patients with Type 2 diabetes and microalbuminuria. Journal of Managed Care Pharmacy 10: 26-32			
Study details	**Population & interventions**	**Costs**[1]	**Outcomes**	**Cost effectiveness**
Economic analysis: Cost utility analysis **Study design:** Decision analytic model **Approach to analysis:** Markov model simulating kidney disease progression through 7 states: normoalbuminuria, microalbuminuria, nephropathy, ESRD (transplant and dialysis), death, cardiovascular disease and withdrawal. The model assumed people in the microalbuminuria and nephropathy states could return to earlier states (improve), once	**Population:** People with type 2 diabetes **Cohort settings** **Intervention 1:** Valsartan **Intervention 2:** Amlodipine	**Total costs (mean per individual):** **Int1:** $92,058 (£92,231) **Int2:** $124,470 (£124,703) **Currency & cost year:** US dollars 2001 **Cost components incorporated:** Study drugs, routine healthcare services to manage	**QALYs (mean per individual):** **Int1:** 6.390 **Int2:** 5.835	**Full incremental analysis:** The intervention using valsartan dominated amlodipine being cheaper and producing more QALYs. **Analysis of uncertainty:** The results were robust to univariate sensitivity analyses on discount rate, health state costs, and medication costs

ESRD was achieved, model progression was unidirectional. **Perspective:** US third party perspective **Time horizon:** 8 years, 3-month cycles **Intervention effect duration:** 8 years **Discounting: C**osts and effects at a 3% annual rate		hypertension, dialysis, renal transplantation		Probabilistic sensitivity analysis was not conducted.
Data sources				
Outcomes: Transition probabilities of withdrawal and transiting from normoalbuminuria used data from the MARVAL study (Viberti 2002, Syne Qua Non 2001). Transition probabilities for the microalbuminuria, nephropathy, ESRD and cardiovascular disease were sourced from additional RCTs in people with nephropathy: Bernner 2001 (losartan versus placebo), Lewis 1993 (captopril versus placebo) and Parving 2001 (ibesartan versus placebo). Transplantation failure was informed by data from the US Renal Data System (2003). **Quality of life weights:** Health state utilities for the renal disease states used values from a published cost-effectiveness analysis of benazepril versus placebo (Hogan 2002). Hogan (2002) cites several primary studies assessing quality of life and health state preferences from people at different states of chronic kidney disease but there is not enough detail to precise the source for each parameter. The utility for the cardiovascular disease state was sourced from a study using a time-trade off methodology to elicit state preferences from US survivors of myocardial infarction (Tsevat 1993). **Costs:** Costs were assumed to increase 2.8% annually based on the consumer price index. Drug costs used prices from the Red Book (2001). The costs of hypertension management appointment used data from insurance company payments (ADP Context 2001). The costs associated with each health state were sourced Brown (1999) who used routine healthcare data to quantify resource use by people with renal and cardiovascular disease in the US. The costs of terminal care (death) used values published from Hogan (2003).				
Comments				
Source of funding: The study was funded by co-authored by the manufacturers of valsartan.				
Overall applicability: Partially applicable				
Analysis conducted 16 years ago from an US third party perspective. The time horizon of the analysis is limited to the 8-year follow-up of the study. No probabilistic sensitivity analysis was conducted.				
Overall quality: Very serious limitations				
Evidence on the efficacy of valsartan is drawn from a single RCT. The analysis does not consider standard care as one of the comparators of interest. The analysis does not consider the lifelong costs as benefits of the comparators. Potential conflict of interest (funded by the manufacturer of valsartan).				

[1]US dollars 2001 converted to sterling 2020 using the EPPI Centre cost converter (accessed 15/01/2020), conversion factor 0.998