Working Title: Cost-effectiveness of dapagliflozin as a treatment for chronic kidney disease: beyond the DAPA-CKD trial

Running title: Cost-effectiveness beyond DAPA-CKD

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Target Journal: TBD

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INTRODUCTION

- The prevalence of chronic kidney disease (CKD) is estimated to be 8–16% worldwide.[1]
- It is a progressive disease resulting from a decline in kidney function, as measured by estimated glomerular filtration rate (eGFR) and accrual of kidney damage, typically identified by the presence of albuminuria.
- Prevalence continues to grow; driven by both ageing populations and an increased prevalence of type 2 diabetes.[1-3]
- Complications associated with CKD include increased risk of all-cause and cardiovascular mortality, kidney disease progression, acute kidney injury, cognitive decline, anaemia, mineral and bone disorders, and fractures[4].
- Subsequently, CKD has a far reaching impact on the individual's quality of life and a substantial societal and economic impact.[5]
- Current treatment options typically include angiotensin-converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), which aim to minimize symptoms and delay disease progression.
- Many patients continue to progress toward advanced CKD. Other treatments providing additional protective efficacy are, therefore, needed to slow CKD progression and protect patients against adverse disease related outcomes.
- data from cardiovascular outcomes trials assessing sodium-glucose co-transporter-2 (SGLT2) inhibitors have demonstrated reno-protective effects distinct from their glucose lowering action, including the potential to reduce the rate of GFR decline and the risk of ESKD in people with type 2 diabetes.[6-12]
- For example, the DECLARE TIMI 58 trial assessed dapagliflozin, an SGLT2 inhibitor, in patients with type 2 diabetes and had or were at risk of atherosclerotic cardiovascular disease.
    - The trial demonstrated that those treated with dapagliflozin had slower rates of kidney decline (hazard ratio, HR: 0.76, 95% confident interval, 95%CI, 0.67-0.87) as

defined the secondary renal composite endpoint (≥40% decrease in eGFR to <60 ml/min per 1.73 m^2, incidence of end-stage kidney disease, ESKD, or death from cardiovascular or kidney-related cause).

- The European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) have approved dapagliflozin as a therapy for patients with CKD (> 15 ml/min per 1.73m^2) - the first available treatment that delays progression to renal failure and cardiovascular and kidney death in patients with CKD, with or without comorbid type 2 diabetes.[13]
- The efficacy and safety of dapagliflozin in addition to standard therapy in patients with CKD and elevated albuminuria (eGFR 25-75 ml/min per 1.73m^2, UACR >200 mg/g).was investigated in the Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD) trial.
    - The trial demonstrated a reduction in the primary composite endpoint of worsening kidney function (defined as a composite of a sustained ≥ 50% eGFR decline, onset of ESKD or death from cardiovascular or kidney-related cause) when treated with dapagliflozin compared to placebo (HR: 0.61, 95%CI, 0.51-0.72, p < 0.001).
    - The trial was ended prematurely due to overwhelming efficacy.
- Subsequently, a cost-effectiveness analysis based on the trial demonstrated cost-effectiveness across multiple European health care systems,[McEwan et al.] and has subsequently been reimbursed across Europe in patients with eGFR between 25 and 75 ml/min per 1.73m^2 with elevated albuminuria (> 200 mg/g).
- The objective is to adapt a previously published Markov model to assess the cost-effectiveness of dapagliflozin in the broader CKD population, including patients without elevated albuminuria in line the EMA/MHRA indications, from European healthcare perspectives in the United Kingdom, Spain and Italy.

METHODS

- DAPA-CKD was a randomised, double-blind, placebo-controlled, event-driven trial in patients with eGFR 25-75 ml/min per 1.73 m^2 and elevated albuminuria (> 200mg/g).
    - The trial investigated the efficacy and safety of dapagliflozin (10 mg once daily) daily versus placebo in addition to current standard therapy, defined as stable dosing of either an ACEi or ARB.
    - The study design, patient characteristics, and outcomes have been published.[14-16]
- The DECLARE TIMI 58 trial was a randomised, double-blind, multinational, placebo-controlled trial in patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease.
    - The study design, patient characteristics, and outcomes have been previously published.[8,17-19]

Economic model

- This analysis adapts a Markov model published in a recent cost effectiveness analysis of dapagliflozin in CKD using patient-level data from the DAPA-CKD trial.[20,21]
- The modelled population considered in this analysis uses the DAPA-CKD and DECLARE trial populations to simulate a broader population according to the regulatory indication of the EMA and MHRA,[13] using patient-level data.
- Outcomes were derived separately for patients with elevated UACR (≥ 200 mg/g) and patients with low UACR (< 200 mg/g), and the two populations were pooled as weighted averages for the broad CKD population (**Error! Reference source not found.**).
    - Results for the low UACR group are thus calculated separately to allow for different methods in estimating the effect of type 2 diabetes.
- The primary model outcome was the incremental cost-effectiveness ratio (ICER), expressed as the difference in costs per quality-adjusted life year (QALY) gained.

- The analysis will also consider the costs avoided through treatment with dapagliflozin in relation to KRT and hospitalisation for heart failure.

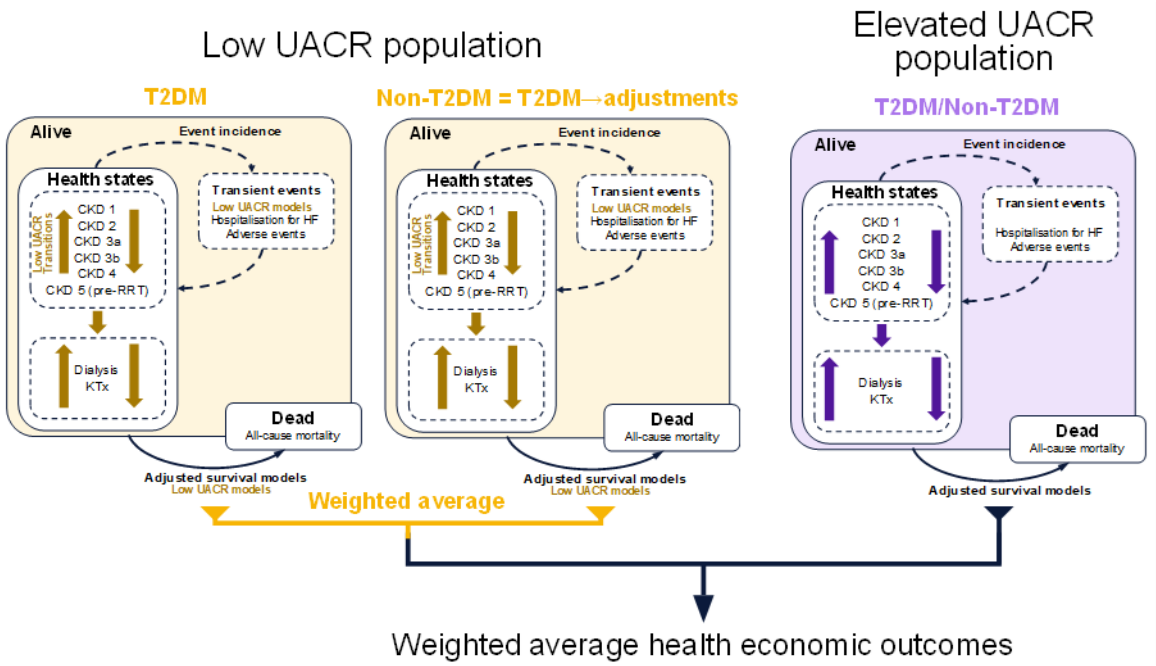

Figure 1. Model schematic for estimation of outcomes in the broad CKD population

Derivation of the broad CKD population

- In the DECLARE TIMI 58 trial, patient CKD status was not among the inclusion or exclusion criteria, meaning a broad range of patients with CKD were eligible for inclusion.[12]
    - Using patient-level data, it was possible to identify a subgroup who would have been diagnosed with CKD according to albuminuria status and CKD-EPI Creatinine Equation ,[22,23] which is referred to hereafter as the $DECLARE_{CKD}$ population.
- To simulate a broader CKD population than what was included in the DAPA-CKD trial, it was assumed to be compatible for analysis with the $DECLARE_{CKD}$ population.
    - The two trials were established with divergent primary endpoints and inclusion/exclusion criteria; to address these differences, the $DECLARE_{CKD}$ population for the present analysis is limited to patients with CKD.
- The threshold for low (<200 mg/g) and elevated (≥200 mg/g) UACR groups is defined according to inclusion criteria of the DAPA-CKD trial.

- The DECLARE TIMI 58 trial did not restrict patients based on UACR status, and analysis revealed the majority to be of have a low UACR.

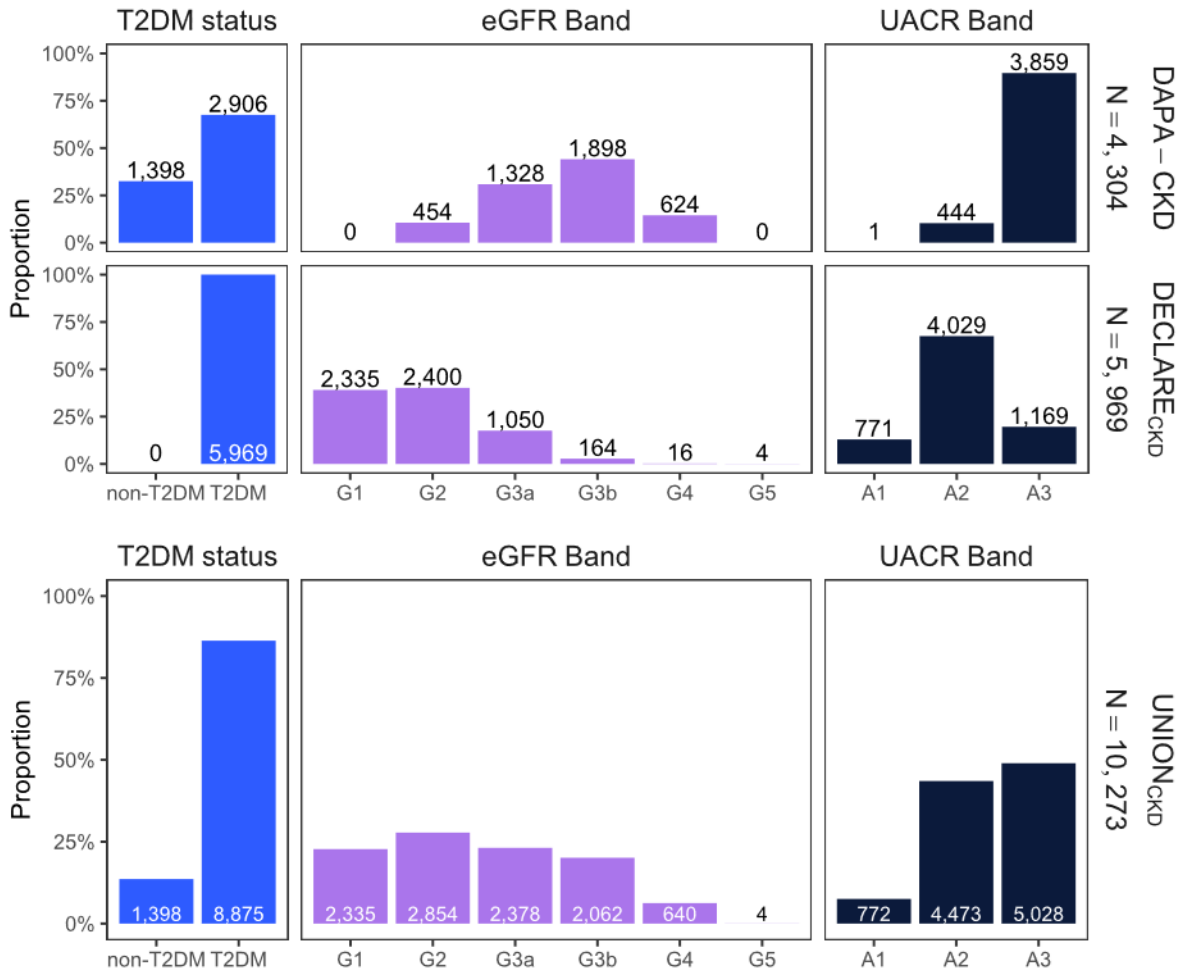

Figure 2. Baseline disease characteristics, stratified by type 2 diabetes status, eGFR and UACR, as defined by KDIGO guidelines. Bars represent proportions while superimposed numbers correspond to patient counts in each category. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes mellitus; UACR, urine albumin creatinine ratio.

Simulated clinical efficacy parameters

- A Poisson simulation extrapolated the treatment effect of dapagliflozin versus placebo into patients with low UACR region and further adjusting the treatment effect patient type 2 diabetes status, independent of treatment received.
- These adjustment factors were applied to the $DECLARE_{CKD}$ data to estimate rates for a non-type 2 diabetes proportion of this low UACR population.

- When considering primary composite endpoint of the DAPA-CKD trial and the non-fatal component endpoints (≥50% sustained eGFR decline or incidence of ESKD), higher UACR was associated with a higher rate of incidence (**Error! Reference source not found.**).
- Patients treated with dapagliflozin were predicted have lower rates of incidence in all patients, regardless of UACR.
- Patients without type 2 diabetes were also expected to incur lower rates of death from any cause (HR: 0.566), hospitalisation for heart failure (HR: 0.302) and incidence of ESKD (HR: 0.995) versus patients with type 2 diabetes.
- In the base case analysis, the model assumes that 75% of the broad CKD population is constituted of patients with low UACR (<200 mg/g) and 25% with elevated UACR (>200 mg/g).

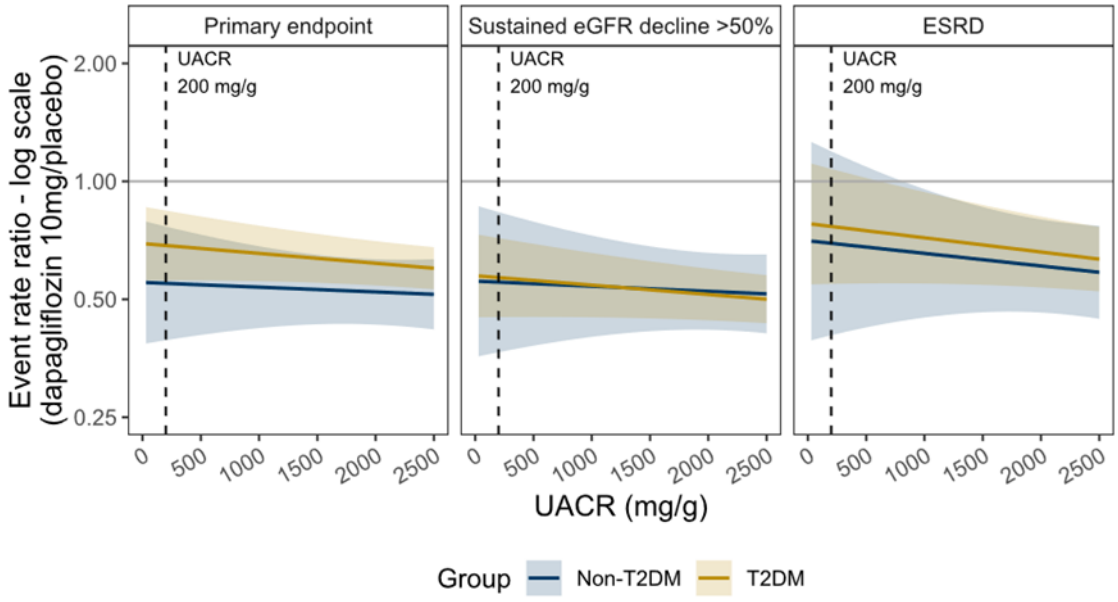

Figure 3. Event rate ratios for the DAPA-CKD primary efficacy endpoint, >50% sustained decline in eGFR, and incidence of ESKD in patients with and without type 2 diabetes treated with dapagliflozin versus placebo. eGFR: estimated glomerular filtration rate; T2DM: type 2 diabetes mellitus; UACR: urine albumin-to-creatinine ratio.

CKD progression

- For patients with elevated UACR, treatment dependent transition matrices were derived from DAPA-CKD trial for the first 4 months of follow-up and from month 4 thereafter, so as to replicate observed patterns of eGFR derived from patient-level data.[14]
    - Insufficient KRT events occurred over the DAPA-CKD trial follow-up period to reliably inform transitions following initiation of these events, so these transitions were informed by the outcomes of a systematic review.[24]
- For patients with low UACR, transition matrices were derived by a similar method, but patients were largely from the DECLARE trial, and the same stratification of matrices for 0 to 4 months and for 4 months onwards was applied.
    - the low UACR transition matrices use DECLARE data for CKD G1-G3 and DAPA-CKD for CKD G4 and G5
- The model derives transitions for post-KRT outcomes from a systematic literature review of CKD modelling methodology as these events were rare in the DECLARE and DAPA-CKD trials.[24]
- To ensure that there was no double counting of mortality, transition probabilities to track disease progression were derived excluding the transition to death.
- The role of altered kidney function on the risk of death was calculated by parametric survival modelling, which is described below.

Mortality and incidence of hospitalisation for heart failure

- The incidence of all-cause mortality was extrapolated using parametric survival equations, in accordance with guidance set out by the National Institute for Health and Care Excellence,[25] fitted to a Weibull distribution.
- To capture the long-term incidence of hospitalisation for heart failure (including first and recurrent events), generalised estimating equations were used with a Poisson distribution.

- All event rate extrapolations were adjusted for baseline patient covariates and treatment arm; eGFR levels were time-updated to reflect increased risk associated with disease progression.
- Analysis was conducted from an intention-to-treat perspective.

Treatment-related adverse events

- Probabilities of serious adverse events or specific adverse events of interest are assessed as a function of number of observed events and patient time at risk.
- Treatment-specific event rates are specified for patients receiving dapagliflozin in addition to standard therapy or standard therapy alone.
- Patients discontinuing treatment with dapagliflozin are subject to the risk of adverse events associated with the placebo arm of DAPA-CKD.
- The model also captures treatment-related adverse events, including volume depletion, major hypoglycaemic events, fractures, diabetic ketoacidosis, and amputation as adverse events.

Treatment discontinuation

- The model assumes a constant rate of discontinuation, which was applied to all patients receiving treatment with dapagliflozin in each modelled cycle.
    - Upon discontinuing treatment with dapagliflozin, patients were assumed to be treated with standard therapy only and subject to the risk of outcomes associated with that treatment arm.

Resource use and costs

- The analysis considered only direct costs from health care payer perspectives in the United Kingdom , Spain and Italy
- Costs were discounted at an annual rate of 3.5% in the United Kingdom and 3% in Spain and Italy, according to local guidelines.[25-27]

- Cost inputs, specific to each country are given in **Error! Reference source not found.**.

Table 1. Cost inputs for the United Kingdom, Spain, and Italy

Health related quality of life

Parameter	United Kingdom (£)	Spain (€)	Italy (€)
Treatment (per annum)			
Dapagliflozin	483[28]	380[]	431[?]
Standard therapy	49[28]	43[]	74[?]
CKD management (per annum)			
CKD G2	1,228[29]	4,633[30]	1,532[31]
CKD G3a	1,228[29]	4,874[30]	1,553[31]
CKD G3b	1,228[29]	4,874[32]	2,256[31]
CKD G4	4,299[29]	5,887[]	3,774[31]
CKD G5, pre-KRT	15,071[29]	9,394[]	4,632[31]
Dialysis	34,579[33]	52,134[]	35,700[34]
Transplant	20,501[?]	24,119[35]	11,197[36]
Transplant (maintenance)	5,831[?]	7,066[37]	73,788[38]
Events			
Hospitalisation for heart failure	5,274[39]	4,450[40]	13,115[41]
Volume depletion	33[42]	39[?]	39[?]
Major hypoglycaemic event	373[43]	336[?]	361[?]
Diabetic ketoacidosis	2,288[44]	4,162[?]	2,312[?]
Fracture	2,570[45]	2,211[?]	2,209[?]
Amputation	13,956[46]	13,816[?]	13,475[?]
CKD: chronic kidney disease; KRT: kidney replacement therapy			

- Utility estimates derived from patient-level EQ-5D-5L data from the DAPA-CKD trial (**Error! Reference source not found.**); further details are available in published material.[McEwan et al.]
- Therefore, the model assumes that patients with low UACR are adequately represented by health-related quality of life outcomes in patients with elevated albuminuria; in effect, that albuminuria has no influence over patient utility.
- Benefits were discounted annually at a rate of 3.5% in the United Kingdom and 3% in Spain and Italy.[25-27]

Table 2. Health state utility values and event-related disutility modifiers for the United Kingdom, Spain, and Italy

Parameter	Utility or Utility Decrement [a]			Source
	United Kingdom	Spain	Italy	
Health-state utility				
CKD G2	0.77 (0.005)	0.83 (0.005)	0.85 (0.09)	DAPA-CKD[47]
CKD G3a	0.77 (0.005)	0.83 (0.005)	0.80 (0.09)	DAPA-CKD[47]
CKD G3b	0.77 (0.005)	0.84 (0.003)	0.80 (0.08)	DAPA-CKD[47]
CKD G4	0.76 (0.006)	0.84 (0.003)	0.74 (0.07)	DAPA-CKD[47]
CKD G5, pre-KRT	0.73 (0.010)	0.83 (0.003)	0.73 (0.07)	DAPA-CKD[47]
Dialysis	0.68 (0.014)	0.79 (0.009)	0.47 (0.05)	DAPA-CKD[47]
Transplant	0.71 (0.070)	0.77 (0.007)	0.71 (0.07)	DAPA-CKD[47]
Event-related disutility modifier				
Hospitalisation for heart failure	-0.09 (0.04)	-0.07 (0.03)	-0.08 (0.04)	DAPA-CKD[47]
Volume depletion	-0.05 (0.01)	-0.01 (0.02)	-0.01 (0.02)	McEwan et al.[49]
Major hypoglycemic events	-0.01 (0.00)	-0.01 (0.00)	-0.01 (0.00)	Beaudet et al.[50]; Currie et al.[51]
Diabetic ketoacidosis	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)	Peasgood et al.[52]
Fracture	-0.09 (0.03)	-0.07 (0.03)	-0.05 (0.03)	DAPA-CKD[47]
Amputation	-0.26 (0.05)	-0.26 (0.05)	-0.32 (0.05)	DAPA-CKD[47]
CKD: chronic kidney disease; KRT: kidney replacement therapy				

Subgroup analysis

- Patients were stratified into populations defined by type 2 diabetes and elevated albuminuria status:
    - Patients with type 2 diabetes and without elevated albuminuria (>200 mg/g)
    - Patients without type 2 diabetes and without elevated albuminuria (<200 mg/g)
    - Patients with type 2 diabetes and with elevated albuminuria (>200 mg/g)
    - Patients without type 2 diabetes and with elevated albuminuria (<200 mg/g)

Sensitivity analysis

- One-way sensitivity analyses were conducted to demonstrate the effect of varying key parameters values on model outcomes.
- Probabilistic sensitivity analysis was conducted to assess uncertainty across all model parameters.

Model Validation

- CKD progression and hospitalisation for heart failure rates for the broad population and subgroups are validated in exercises described in the supplementary material, which demonstrate that the model simulates realistic outcomes.

RESULTS

Base case analysis

- Patients treated with dapagliflozin in addition to standard therapy were expected to experience a slower rate of CKD progression and reduced rates of hospitalisation for heart failure, leading to improved life expectancy versus patients treated with standard therapy alone.
- Across all considered countries, mean life expectancy (undiscounted) in the overall broad population was extended by 0.6 years in those treated with dapagliflozin (12.5 years) versus those treated with standard therapy alone (11.9 years).
- Patients treated with dapagliflozin would spend more time in early stages of CKD (stages G1 to G4) versus those treated with standard therapy alone (dapagliflozin: 14.5 years; standard therapy 13.4 years).
- However, patients spent a comparable length of time in ESKD health states (CKD G5, dialysis, and transplant) in both treatment groups (dapagliflozin: 0.67 years; standard therapy: 0.70 years).
- Patients treated with dapagliflozin had a lower rate of hospitalisation for heart failure (119 vs 140 events per 1000 patients)

Table 3. Base case clinical outcomes for the broad CKD population

Outcome	Dapagliflozin plus Standard Therapy	Standard Therapy	Incremental
Total LYs gained, undiscounted	12.51	11.91	0.60
Mean time in each CKD stage, yr.			
CKD G1	2.91	2.56	0.35
CKD G2	6.04	5.60	0.43
CKD G3	3.27	3.07	0.20
CKD G4	2.30	2.13	0.17
CKD G5 (pre-KRT)	1.20	1.22	-0.01
Dialysis	0.17	0.18	-0.01
Transplant	0.67	0.70	-0.03
Event incidence, per 1000 patients			
Hospitalisation for heart failure	119	140	-21
Adverse events [a]	TBD	TBD	TBD
[a] Adverse events include volume depletion, hypoglycemic events, fractures, diabetic ketoacidosis, and amputation.			

- Treatment with dapagliflozin in the broad CKD population led to lifetime QALY gains of 0.47, 0.51, and 0.52 in the United Kingdom, Spain, and Italy, respectively (Table 4).
    - Differences between setting are borne of the application of country specific utility tariffs, life tables, and discounting rates.
- Treatment with dapagliflozin led to increased overall costs versus placebo in the United Kingdom (£3,213), Spain (€4,164), and Italy (€2,616).
    - The main contributors of additional cost in those treated with dapagliflozin were additional drug acquisition costs and disease management costs resulting from extended life expectancy.
    - These costs were partially offset by reductions in costs associated with KRT through delayed time to dialysis or transplant, and a reduced rate of hospitalisation for heart failure over the modelled period (lifetime).
    - Most of these cost offsets as a result of treatment with dapagliflozin were accrued during the first 15 years from baseline (Figure 4).
    - Beyond this point, the incremental costs associated with KRT from treatment with dapagliflozin reduced as the proportion of patients in the control arm progressing to ESKD will have reduced, relative to dapagliflozin, after approximately 15 years.
- Dapagliflozin was considered cost-effective with ICERs well below the specified willingness-to-pay thresholds at £6,846/QALY, €8,245/QALY, and €5,018/QALY in the United Kingdom, Spain, and Italy.

Table 4. Base case health economic outcomes for the broad CKD population in the United Kingdom, Spain, and Italy

Outcome	Dapagliflozin plus Standard Therapy	Standard Therapy	Incremental
United Kingdom, £			
Total costs	42,097	38,884	3,213
Drug acquisition	4,505	571	3,934
CKD management (pre-KRT)	18,506	17,996	510
KRT	16,466	17,646	-1,180
Hospitalisation for heart failure	418	511	-93
Adverse events	2,202	2,159	42
Total QALYs gained	9.56	9.09	0.47
ICER, £/QALY			6,846
Spain, €			
Total costs	88,808	84,645	4,164
Drug acquisition	3,450	515	2,935
CKD management (pre-KRT)	57,427	54,430	2,997
KRT	24,902	26,715	-1,813
Hospitalisation for heart failure	363	444	-81
Adverse events	2,666	2,540	126
Total QALYs gained	10.31	9.80	0.51
ICER, €/QALY			8,245
Italy, €			
Total costs	49,382	46,766	2,616
Drug acquisition	4,233	883	3,351
CKD management (pre-KRT)	21,218	20,313	905
Dialysis	20,647	22,094	-1,446
Hospitalisation for heart failure	1,078	1,316	-238
Adverse events	2,207	2,162	45
Total QALYs gained	10.27	9.75	0.52
ICER, €/QALY			5,018

CKD: chronic kidney disease; ICER: incremental cost-effectiveness ratio; KRT: kidney replacement therapy; QALY: quality-adjusted life year

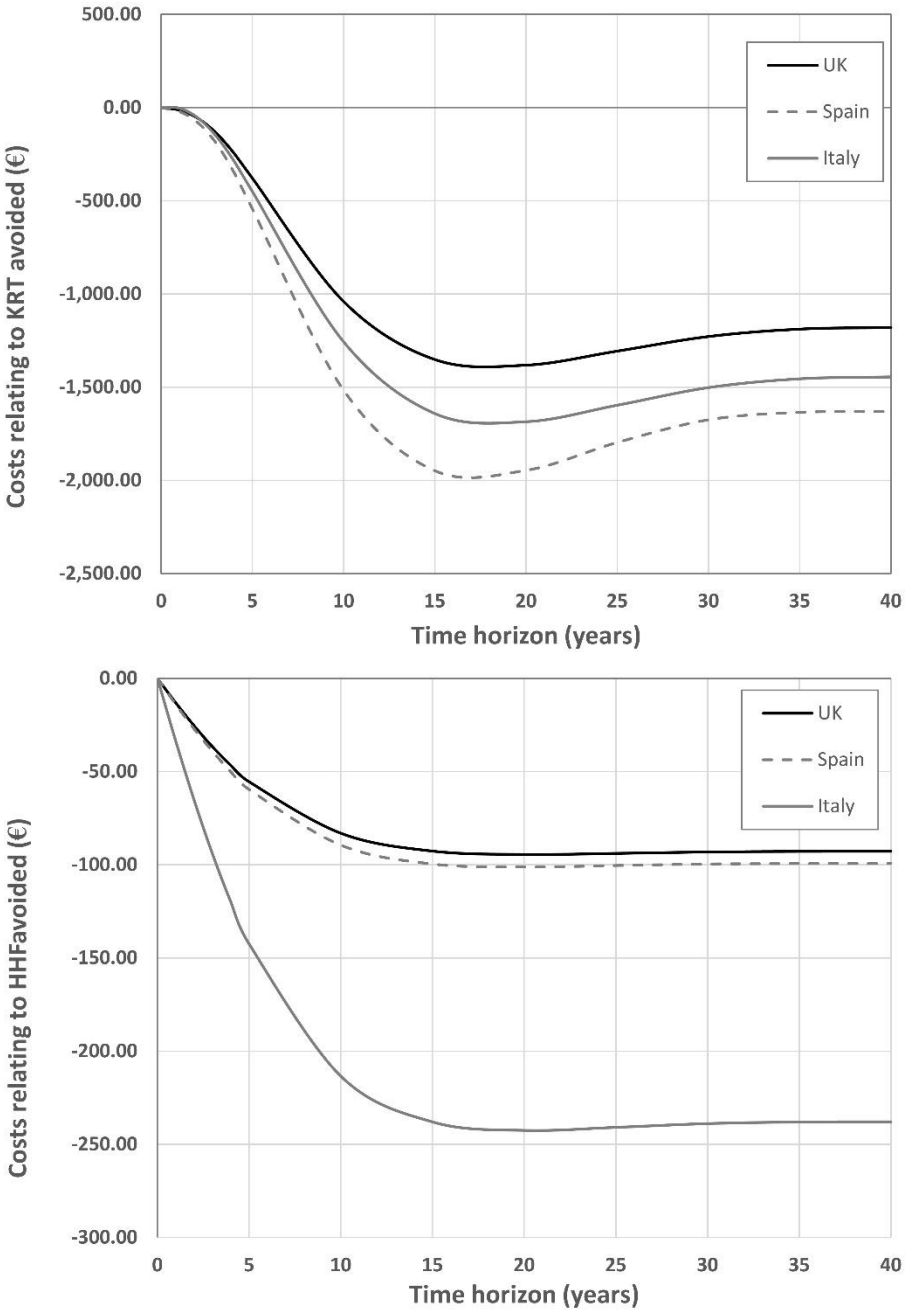

Figure 4. Incremental costs (in Euros) associated with (a) kidney replacement therapy, (b) hospitalisation for heart failure avoided as a result of treatment with dapagliflozin and standard therapy versus standard therapy alone

Subgroup analysis

- Results show that dapagliflozin is cost effective in all tested settings compared to standard therapy alone, regardless of UACR or type 2 diabetes status (Figure 5).
- In all subgroup settings, the costs associated with the treatment and placebo arms of the low UACR group were lower than those with elevated UACR.

  However, the ICERs between the treatment and placebo arms of the low UACR group were greater than the base case ICERs, with those in the elevated UACR group smaller.

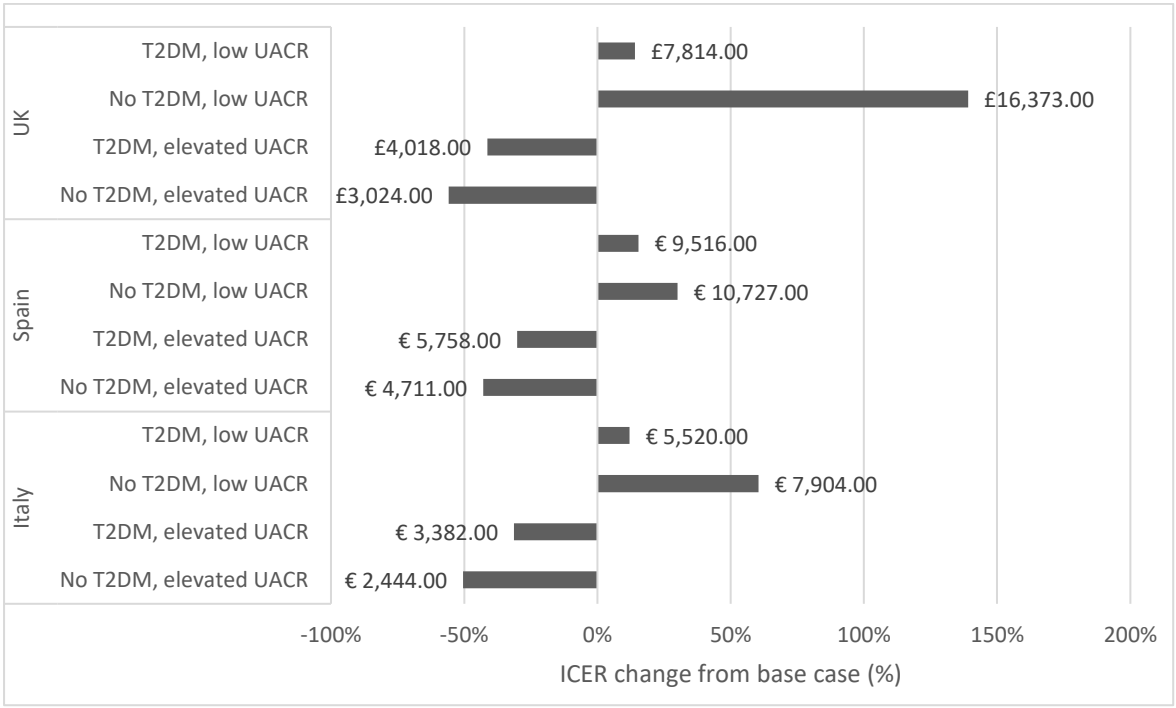

Figure 5. Subgroup analysis of patients treated with dapagliflozin and standard therapy versus standard therapy alone based on type 2 diabetes status and UACR (<200 mg/g, >200 mg/g) in the United Kingdom, Spain, and Italy

Deterministic sensitivity analysis

- Deterministic sensitivity analyses showed that results were robust to the choice of input parameters, with ICERs most positively influenced by shorter time horizons (10 years) and negatively influenced by lower cost discounting (0%).
- However, analyses remained cost effective for all parameter variations.

Probabilistic sensitivity analysis

- Probabilistic sensitivity analysis demonstrated that the model was robust to joint uncertainty of all parameters.
- In the United Kingdom, 99.6% of simulations were found to be cost effective at a threshold of £20,000/QALY, 100 % were cost effective at a threshold of €30,000/QALY in Spain, and 100 % were cost effective at a threshold of €25,000/QALY in Italy (Figure 6).

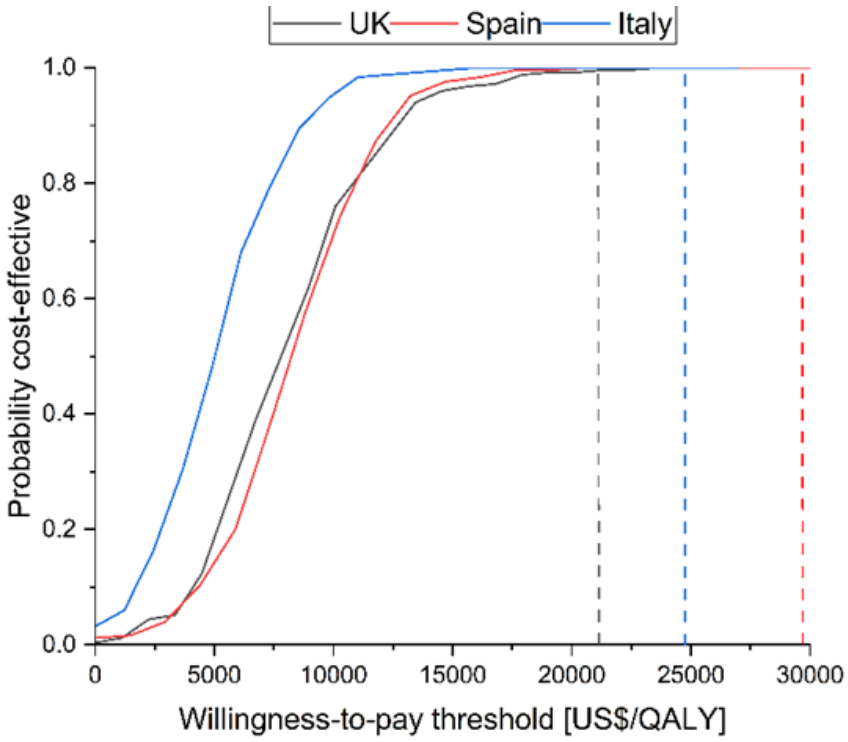

Figure 6. Cost-effectiveness acceptability curves for the United Kingdom, Spain, and Italy

DISCUSSION

- Using a previously published model, this study bridges a significant data gap in the treatment of CKD, simulating clinical outcomes in patients beyond the DAPA-CKD trial to the broader CKD population for which dapagliflozin is approved in CKD.
    - Extrapolation using this simulated population showed that dapagliflozin slowed the progression of CKD, extended life expectancy and reduced the incidence of hospitalisation for heart failure in this broader CKD population.
- Patients with elevated UACR were generally expected to have a higher rate of progression of chronic kidney disease, including a greater proportion of patients reaching ESKD.
    - Dapagliflozin had greater expected efficacy in these patients, resulting in greater quality of life benefits than for the low UACR population.
    - Hence, in these results, dapagliflozin may have demonstrated a greater cost effectiveness in the high UACR population.
- The key findings in this analysis demonstrate that clinical and economic outcomes demonstrated in the DAPA-CKD trial population may be generalisable to a broader population with less severe albuminuria.
    - In line with the DAPA-CKD cost effectiveness analysis, patients treated with dapagliflozin spent more time in CKD stages 1-4 (0.70 years versus 0.87 years in the DAPA-CKD population) but similar lengths of time in the ESKD health states in both treatment arms (-0.02 years versus -0.04 years).
    - In both analyses, treatment with dapagliflozin led to an increase in life expectancy, though there was a less pronounced increase in the broader population (1.75 years versus 0.60 years).
    - This is in line with expectations, given that the broad population extends to patients who have less severe kidney damage.

- Nevertheless, the clinical outcomes from treatment with dapagliflozin still led to ICERs in all countries considered in the United Kingdom, Spain and Italy that could be considered to represent good value.
    - This conclusion was also reached in all subgroup analyses considering patients with or without type 2 diabetes and the degree of albuminuria.

- This cost-effectiveness analysis is subject, as with any modelling analysis, to several limitations.
- First, any extrapolations beyond trial follow-up periods are subject to uncertainty, and this analysis may be considered to have considerable additional uncertainty resulting from insufficient evidence to inform outcomes in patients without type 2 diabetes and with low UACR.
- Second, the analysis assumed that discrete eGFR-defined states capture patient heterogeneity, which may be considered to be in accordance with clinical guidelines for the management of CKD.[22,53]
- Third, DAPA-CKD and DECLARE TIMI 58 trial data could not be used to simulate outcomes in patients who initiated kidney replacement therapy due to insufficient data.
    - Therefore, the transition probabilities for post-KRT outcomes applied in the model were estimated in a published systematic review of modelling in CKD.[24]
- Finally, while this analysis takes advantage of two trial datasets to generate a simulated dataset that includes patient-level data from 10,273 patients, the expanded population included healthier patients in relation to kidney function.
    - Therefore, the overall time to progress to advanced CKD is therefore greater than for the DAPA-CKD trial population. As a result, the length of follow-up limits the predictive power of the broad population dataset.

- In conclusion, the outcomes estimated from this analysis address a data gap that currently exists in patients with CKD according to the regulatory indication by EMA and MHRA.
    - By incorporating patient-level data from the DAPA-CKD trial and DECLARE TIMI 58 trial, this economic analysis demonstrates that the value of dapagliflozin to patients with CKD and payers, may be broader than what has previously been demonstrated.
    - The country-specific results of the model suggest that dapagliflozin could be a cost-effective treatment option for the broad CKD population and all subgroups in Spain, Italy and the UK.

REFERENCES

1. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):260-72.
2. Midtvedt K, Heldal K. Chronic kidney disease and the aging population. Transplantation. 2014;97(11):e64.
3. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat Rev Nephrol. 2016;12(2):73-81.
4. Thomas R, Kanso A, Sedor JR. Chronic kidney disease and its complications. Prim Care. 2008;35(2):329-44, vii.
5. Vanholder R, Annemans L, Brown E, et al. Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. Nature Reviews Nephrology. 2017;13(7):393.
6. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016;375(4):323-34.
7. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017;377(7):644-57.
8. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-57.
9. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine. 2019;381(21):1995-2008.
10. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28.
11. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-24.
12. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. Lancet Diabetes Endocrinol. 2019;7(8):606-17.
13. European Medicines Agency. Forxiga 5mg film-coated tablets - Summary of Product Characteristics. 2022. Available at: https://www.medicines.org.uk/emc/product/2865/ [Accessed 17/10/2022].
14. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. New England Journal of Medicine. 2020;383(15):1436-46.
15. Wheeler DC, Stefansson BV, Batiushin M, et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics. Nephrology Dialysis Transplantation. 2020;35(10):1700-11.
16. Heerspink HJL, Stefansson BV, Chertow GM, et al. Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. Nephrology Dialysis Transplantation. 2020;35(2):274-82.
17. Wiviott SD, Raz I, Bonaca MP, et al. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)–TIMI 58 Trial. American Heart Journal. 2018;200:83-9.
18. Raz I, Mosenzon O, Bonaca MP, et al. DECLARE-TIMI 58: Participants' baseline characteristics. Diabetes, Obesity and Metabolism. 2018;20(5):1102-10.
19. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE–TIMI 58 randomised trial. The Lancet Diabetes & Endocrinology. 2019;7(8):606-17.
20. McEwan P, Darlington O, Wheeler D, et al. POS-335 COST-EFFECTIVENESS OF DAPAGLIFLOZIN AS A TREATMENT FOR CHRONIC KIDNEY DISEASE: A HEALTH-ECONOMIC ANALYSIS OF DAPA-CKD. Kidney International Reports. 2021;6(4):S145-S6.
21. National Institiute for Health and Care Excellence. Dapagliflozin for treating chronic kidney disease [TA775]. 2022. Available at: https://www.nice.org.uk/guidance/TA775 [Accessed 17/10/2022].

22. Eknoyan G, Lameire N, Eckardt K, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3(1):5-14.
23. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
24. Sugrue DM, Ward T, Rai S, et al. Economic Modelling of Chronic Kidney Disease: A Systematic Literature Review to Inform Conceptual Model Design. PharmacoEconomics. 2019;37(12):1451-68.
25. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013. Available at: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 [Accessed 17/10/2022].
26. López-Bastida J, Oliva J, Antoñanzas F, et al. Spanish recommendations on economic evaluation of health technologies. The European Journal of Health Economics. 2010;11(5):513-20.
27. Agenzie Italiana del Farmaco. Linee Guida Per La Compilazione Del Dossier A Supporto Della Domanda Di Rimborsabilità E Prezzo Di Un Medicinale. 2019. Available at: https://www.aifa.gov.it/documents/20142/1307543/2021.01.22_estratto_linee_guida_sezione_E.pdf [Accessed 21/10/2022].
28. Haymarket Media Group. Database of Prescription and Generic Drugs, Clinical Guidelines. Monthly Index of Medical Specialities. 2020; Updated 28 October 2020. Available from: https://www.mims.co.uk/.
29. Kent S, Schlackow I, Lozano-Kühne J, et al. What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? BMC Nephrology. 2015;16(1):65.
30. Darbà J, Marsà A. Chronic kidney disease in Spain: analysis of patient characteristics, incidence and direct medical costs (2011–2017). Journal of Medical Economics. 2020:1-7.
31. Jommi C, Armeni P, Battista M, et al. The Cost of Patients with Chronic Kidney Failure Before Dialysis: Results from the IRIDE Observational Study. Pharmacoecon Open. 2018;2(4):459-67.
32. Lorenzo-Sellares V, Pedrosa MI, Santana-Expósito B, et al. Análisis de costes y perfil sociocultural del enfermo renal: impacto de la modalidad de tratamiento. Nefrología (Madrid). 2014;34:458-68.
33. National Institute for Health and Care Excellence. Renal replacement therapy and conservative management. NICE guideline [NG107]. 2018. Available at: https://www.nice.org.uk/guidance/ng107 [Accessed 28 October 2020].
34. Vaccaro CM, Sopranzi F. A comparison between the costs of dialysis treatments in Marche Region, Italy: Macerata and Tolentino hospitals. Annali dell'Istituto Superiore di Sanità. 2017;53(4):344-9.
35. Sanidad. Md. Hospital discharge records in the national health system. 2021. Available at: https://www.sanidad.gob.es/en/estadEstudios/estadisticas/cmbdhome.htm [Accessed 01/02/2022].
36. Roggeri DP, Roggeri A, Zocchetti C, et al. Healthcare Resource Consumption And Costs Before And After Kidney Transplantation In Lombardy, Italy. Value in Health. 2015;18(7):A513-A4.
37. Arrieta J, Rodríguez-Carmona A, Remón C, et al. La diálisis peritoneal es la mejor alternativa coste-efectiva para la sostenibilidad del tratamiento con diálisis. Nefrología (Madrid). 2011;31:505-13.
38. Cavallo MC, Sepe V, Conte F, et al. Cost-Effectiveness of Kidney Transplantation From DCD in Italy. Transplantation Proceedings. 2014;46(10):3289-96.
39. Kent S, Briggs A, Eckermann S, et al. Are value of information methods ready for prime time? An application to alternative treatment strategies for NSTEMI patients. Int J Technol Assess Health Care. 2013;29(4):435-42.

40. Farré N, Vela E, Clèries M, et al. Real world heart failure epidemiology and outcome: A population-based analysis of 88,195 patients. PLoS One. 2017;12(2):e0172745.
41. Maggioni AP, Orso F, Calabria S, et al. The real-world evidence of heart failure: findings from 41 413 patients of the ARNO database. Eur J Heart Fail. 2016;18(4):402-10.
42. Personal Social Services Research Unit. Unit Costs of Health and Social Care. 2020; Updated 28 October 2020. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/.
43. Hammer M, Lammert M, Mejías SM, et al. Costs of managing severe hypoglycaemia in three European countries. Journal of Medical Economics. 2009;12(4):281-90.
44. Dhatariya KK, Skedgel C, Fordham R. The cost of treating diabetic ketoacidosis in the UK: a national survey of hospital resource use. Diabetic Medicine. 2017;34(10):1361-6.
45. Department of Health. NHS reference costs 2019 to 2020. 2020; Updated 28 October 2020. Available from: https://www.england.nhs.uk/national-cost-collection/.
46. Alva ML, Gray A, Mihaylova B, et al. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabetic Medicine. 2015;32(4):459-66.
47. AstraZeneca. A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD). 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT03036150 [accessed 04 June 2020].
48. Lee AJ, Morgan CL, Conway P, et al. Characterisation and comparison of health-related quality of life for patients with renal failure. Curr Med Res Opin. 2005;21(11):1777-83.
49. McEwan P, Darlington O, McMurray JJV, et al. Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. European Journal of Heart Failure.22:2147–56.
50. Beaudet A, Clegg J, Thuresson PO, et al. Review of utility values for economic modeling in type 2 diabetes. Value Health. 2014;17(4):462-70.
51. Currie CJ, Morgan CL, Poole CD, et al. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Current Medical Research and Opinion. 2006;22(8):1523-34.
52. Peasgood T, Brennan A, Mansell P, et al. The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes. Med Decis Making. 2016;36(8):1020-33.
53. National Institute for Health and Care Excellence. Chronic kidney disease: assessment and management. NICE guideline [NG203]. 2021. Available at: https://www.nice.org.uk/guidance/ng107 [Accessed 26 October 2022].