Scientific Research Publishing

Open Journal of Nephrology, 2023, 13, 435-450
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

Cost Utility Analysis of Dapagliflozin in Egyptian Patients with CKD from the Payer Perspective

Gamal Saadi[1], Magdy Elsharkawy[2], Gamal Fathy El-Naggar[3], Ahmed F. Elkeraie[4], Emad R. Issak[5*]

[1]Department of Nephrology, Faculty of Medicine Kasr Al-Aini, Cairo University, Cairo, Egypt
[2]Department of Nephrology, Faculty of Medicine, Ain-Shams University, Cairo, Egypt
[3]Department of Nephrology, Faculty of Medicine, Tanta University, Tanta, Egypt
[4]Department of Nephrology, Faculty of Medicine, Alexandria University, Alexandria, Egypt
[5]Department of Internal Medicine, Faculty of Medicine, Ain-Shams University, Cairo, Egypt
Email: *dr.emad.r.h.issak@gmail.com

How to cite this paper: Saadi, G., Elsharkawy, M., El-Naggar, G.F., Elkeraie, A.F. and Issak, E.R. (2023) Cost Utility Analysis of Dapagliflozin in Egyptian Patients with CKD from the Payer Perspective. *Open Journal of Nephrology*, **13**, 435-450.
https://doi.org/10.4236/ojneph.2023.134040

Received: November 1, 2023
Accepted: December 15, 2023
Published: December 18, 2023

Abstract

Background: Chronic kidney disease is a serious public health issue in Egypt. An estimated 13% of individuals in Egypt are expected to have CKD, with a higher prevalence among older adults and in rural regions. The primary goal of the study was to compare the cost-utility of the standard of care alone against add-on medication, dapagliflozin, as a preventative measure against complications of CKD in cases with or without diabetes mellitus. **Methods:** A lifetime Markov state transition model with a 3-month cycle was employed based on the clinical evidence from the DAPA-CKD clinical trial. The model was to provide estimates of the long-term economic and health impact of managing CKD patients. Cost-effectiveness is assessed regarding the cost per quality-adjusted life year (QALY) gained. This economic evaluation study used a payer perspective. Moreover, the study evaluated the impact on the budget due to the undertaking of dapagliflozin. One-way deterministic sensitivity analyses, as well as a probabilistic sensitivity analysis, were employed. **Results:** During a lifetime horizon, the difference in cost between dapagliflozin and SOC was EGP −65,212 (USD 2126.89). The difference in QALY between dapagliflozin and SOC was 4.3. In CKD patients, adding dapagliflozin to ramipril generates better QALYs and lower costs than ramipril alone. Dapagliflozin improved the outcomes and generated cost savings. A deterministic one was sensitivity analysis revealed that the model is robust to changes in all variables included. Probabilistic sensitivity analysis using Monte Carlo simulation with 10,000 iterations showed that in about 82.64% of trials, dapag-

liflozin is cost-saving. The undertaking of dapagliflozin by any percent will have a positive impact on the budget. **Conclusion:** During the lifetime horizon, dapagliflozin is cost-saving; it benefits the quality of life and the total cost. The addition of dapagliflozin to SOC has a saving effect of 11.9% of the budget.

Keywords

Chronic Kidney Disease, Sodium-Glucose Cotransporter-2 Inhibitors, Dapagliflozin, Cost-Utility, Budget Impact

1. Introduction

Chronic kidney disease (CKD) is a progressive loss of renal function over months or years [1]. The prevalence rates of CKD worldwide are high and have increased in the last decade to about 13% - 15%, with an increased prevalence of diabetes (DM) and hypertension [2]. According to a recent systematic review, the prevalence of CKD among adults with DM, hypertension, and obesity was 31%, 27%, and 14%, respectively [3].

Chronic kidney disease (CKD) has become a significant public health issue. It is a global cause of morbidity and mortality [4]. In 2016, CKD was reviewed as the 16th leading cause of death and was forecasted to increase to the fifth top cause by 2040 [5]. Over the past 30 years, CKD has been considered among the top ten contributors to global loss of health and the increasing global burden of disease (GBD) among older adults [6]. Based on the global health estimated report of the World Health Organization (WHO), CKD was the 10th cause of global death in 2019 [7]. It represents a considerable burden, especially in developing countries, due to the high prevalence of uncontrolled chronic risk factors, such as obesity, cardiovascular disease (CVD), and diabetes [8].

In Egypt, CKD is a significant public health problem. According to a recent study, the prevalence of CKD in Egypt was estimated to be around 13% of adults, with a higher prevalence in rural areas and among older adults [1] [9].

The leading causes of CKD in Egypt include diabetes, hypertension, and glomerulonephritis. The burden of CKD in Egypt is further compounded by limited access to healthcare services, inadequate screening and detection of CKD, and a shortage of effective treatment [10].

Dapagliflozin Technology

Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor used orally in managing T2DM. It decreased renal glucose reabsorption by inhibiting the transporter protein SGLT2 in the renal proximal tubule.

Plentiful, well-designed clinical trials with dapagliflozin, either as add-on therapy or monotherapy, have demonstrated reductions in HBA1c and fasting plasma

glucose levels [11]. Dapagliflozin is reported as the only SGLT2 inhibitor to demonstrate a significantly reduced risk of CV death vs. placebo in patients with HFrEF [12]. After that success in patients with HFrEF Worldwide and in Egypt [13], dapagliflozin has emerged as a promising class of medications for treating HFpEF.

Moreover, dapagliflozin showed a kidney protective effect in patients with or without T2DM in the DAPA-CKD trial [14]. DAPA CKD, an international, phase-3, multicentre, double-blind, randomized controlled trial (RCT), evaluated the safety and efficacy of dapagliflozin as an add-on therapy to standard of care (SoC) to prevent CKD progression or mortality due to renal or CV causes among patients with CKD, with or without type 2 diabetes [14]. The available treatment options for CKD are considered to be limited. Experts recommend angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) as the gold standard to slow the progression of the disease [15].

Nonetheless, healthcare decision-makers require decision-making support tools validated to evaluate the expected long-term economic outcomes associated with CKD management.

2. Objective

The main objective behind conducting this economic model was to evaluate the cost-utility of dapagliflozin as an add-on therapy to standard of care SOC (ramipril) versus ramipril alone as a preventative strategy against CKD complications with or without the presence of DM from the payer perspective over a lifetime horizon to guide decision-makers to the best available therapy for this population. To the best of our knowledge, this is the first economic model built to evaluate the cost-effectiveness of dapagliflozin in Egyptian CKD patients. Moreover, the study evaluated the impact on the budget due to the undertaking of dapagliflozin.

3. Methods

3.1. The Model Population

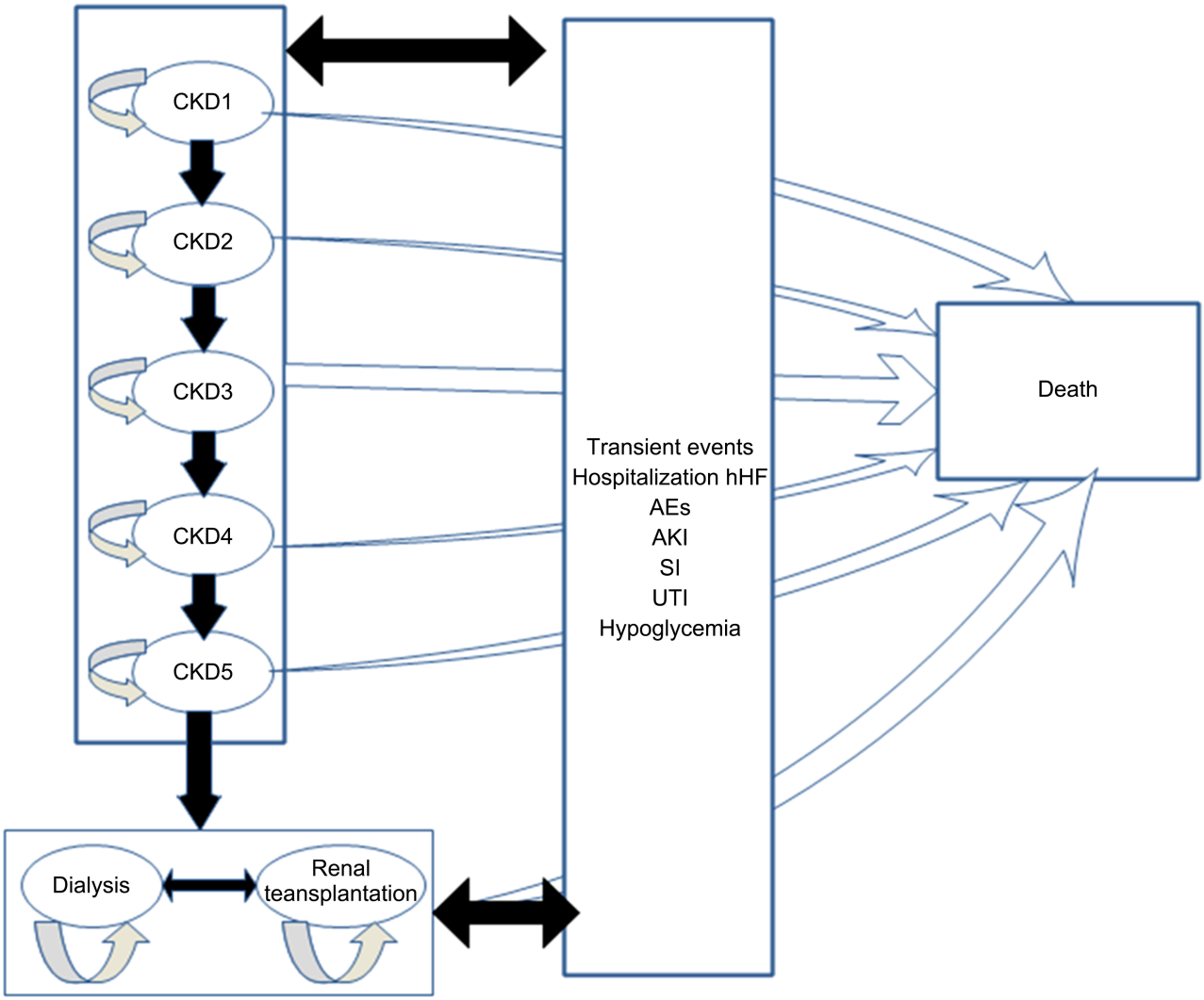
The model population reflects the participants included in the DAPA-CKD clinical trial [14]. In brief, the eligible patients were adults with or without T2DM who had an eGFR of 25 - 75 mL per min per 1.73 m^2 of body surface area and a urinary albumin-to-creatinine ratio of 200 - 5000 mg/g. The starting age in this study was 60 years.

3.2. Intervention and Comparator

The intervention in this study was dapagliflozin (10 mg once daily) as an add-on to the current background therapy or SOC. The SOC was to maintain patients with a stable, optimized dose of ramipril 5 mg, an angiotensin-converting enzyme inhibitor (ACEI). Patients in the dapagliflozin group received an optimized dose of ramipril similar to those in the SOC group.

3.3. Model Overview

A lifetime Markov state transition model with a 3-month cycle was employed based on the clinical evidence from the DAPA-CKD clinical trial [14]. The model health states were defined by CKD state from stage 1 to stage 5 and ESKD, which was stratified into dialysis and transplant based on progression events observed in the DAPA-CKD clinical trial (**Figure 1**). The cohort population was distributed across all available CKD stages at baseline, consistent with the baseline population characteristic of the DAPA-CKD clinical trial, which was 11%, 31%, 44%, and 14% in CKD stage 2, stage 3a, stage 3b, and stage 4, respectively [14]. There were no patients in CKD stage 1, stage 5, or dialysis at the beginning. All patients eventually would enter the absorbing health state, which is the death state.



Note: CKD 1: chronic kidney disease stage 1; CKD 2: chronic kidney disease stage 2; CKD 3a: chronic kidney disease stage 3a; CKD 3b: chronic kidney disease stage 3b; CKD 4: chronic kidney disease stage 4; CKD 5: chronic kidney disease stage 5; ESKD: end stage kidney disease; AEs: adverse events; AKI: acute kidney injury; GI: genital infection; UTI: urinary tract infection.

Figure 1. Model schematic of patients with CKD.

The model has been designed to provide estimates of the long-term economic and health impact of managing CKD patients. Cost-effectiveness is assessed in terms of the cost per quality-adjusted life year (QALY) gained (*i.e.* how much it costs for one year of life at full health). Patients are simulated as shown in the model schematic diagram (**Figure 1**). Each simulated subject is progressed through the model in 3-monthly time increments.

3.4. Model Inputs Data

Transition probabilities between different health states are based on data from the DAPA-CKD. Transitions were split into months 0 - 4 and months four onwards to capture the change in trend observed in mean eGFR in the DAPA-CKD clinical trial [5]. Rates of other adverse events not mentioned in DAPA-CKD are derived from recent studies of dapagliflozin [16] [17]. All clinical data, as well as utility data, are shown in **Table 1** and **Table 2**.

Due to a paucity of utility data in the Egyptian setting, the utility data from published studies was used [18]-[23]. All utility data are shown in **Table 2**.

This economic evaluation study used a payer perspective. Direct costs included the acquisition cost of dapagliflozin, the cost of CKD treatment, and the cost of adverse event treatment. In addition, other direct costs related to outpatient visits, such as laboratories and monitoring, were added. The total monthly cost for dapagliflozin was calculated based on daily dose and unit cost. The daily dose used in this study was similar to that used in the DAPA-CKD clinical trial [14]. The median price of dapagliflozin was 333 EGP (10.86 USD) per month. All cost data are shown in **Table 3**.

3.5. Model Process and Analyses

Patients are simulated until death or the lifetime horizon. Once all patients have been simulated, the relevant statistics are summarized and presented. Of particular interest are the total costs and QALYs over the simulated time horizon (including those associated with complications, treatment, and adverse events), which are used to estimate cost-utility. The study's perspective is the payer perspective to maximize health gain for the patients while ensuring the most efficient use of healthcare resources. The time horizon for the study is a lifetime. All costs and effects were discounted at 3.5% annually. The model is localized to the actual practice in Egypt.

The Markov model was built into Microsoft Excel 2019 (Microsoft, Redmond, WA, USA). The predicted long-term outcomes and costs were estimated and discounted at 3.5% as recommended by the ISPOR Health Economic Evaluation guideline [24]. The incremental cost-effectiveness ratio (ICER) was calculated using the formula ICER = (total cost of dapagliflozin cohort − total cost of SOC cohort)/(effect of dapagliflozin cohort − effect of SOC cohort), where the effect is quality-adjusted life year (QALY). Furthermore, the impact on the budget was calculated as a percent change due to the penetration of dapagliflozin by different percentages.

Table 1. Transition probabilities included in the analysis.

Dapagliflozin																	
From/to	CKD 1		CKD 2		CKD 3a		CKD 3b		CKD 4		CKD 5		Dialysis		Transplantation		Ref.
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Month 0 - 4																	
CKD 1	0.586	0.076	0.219	0.064	0.049	0.033	0.049	0.033	0.024	0.024	0.024	0.024	0.024	0.024	0.025	0.024	[14]
CKD 2	0.018	0.005	0.709	0.016	0.246	0.015	0.019	0.005	0.003	0.002	0.003	0.002	0.001	0.001	0.001	0.001	[14]
CKD 3a	0.001	0.001	0.079	0.006	0.749	0.009	0.162	0.008	0.008	0.002	0	0	0	0	0	0	[14]
CKD 3b	0.001	0	0.005	0.001	0.079	0.004	0.812	0.006	0.102	0.005	0.001	0	0	0	0	0	[14]
CKD 4	0.001	0.001	0.003	0.001	0.006	0.002	0.143	0.008	0.843	0.008	0.004	0.001	0.001	0.001	0.001	0	[14]
CKD 5	0.063	0.06	0.125	0.08	0.062	0.058	0.124	0.08	0.375	0.118	0.125	0.08	0.063	0.059	0.062	0.059	[14]
Dialysis	0	0	0	0	0	0	0	0	0	0	0	0	0.995	0.0995	0.005	0.0005	[17]
Transplantation	0	0	0	0	0	0	0	0	0	0	0	0	0.007	0.0007	0.993	0.0993	[17]
Month 5 & on																	
CKD 1	0.891	0.017	0.07	0.014	0.009	0.005	0.015	0.007	0.006	0.004	0.003	0.003	0.003	0.003	0.003	0.003	[14]
CKD 2	0.005	0.001	0.909	0.004	0.078	0.004	0.006	0.001	0.002	0.001	0	0	0	0	0	0	[14]
CKD 3a	0.001	0	0.025	0.001	0.913	0.003	0.059	0.002	0.002	0	0	0	0	0	0	0	[14]
CKD 3b	0	0	0.001	0	0.025	0.001	0.938	0.002	0.035	0.001	0	0	0	0	0	0	[14]
CKD 4	0	0	0	0	0.001	0	0.035	0.002	0.952	0.002	0.01	0.001	0.001	0	0	0	[14]
CKD 5	0.001	0.001	0.002	0.001	0.002	0.001	0.001	0.001	0.027	0.005	0.92	0.008	0.045	0.006	0.002	0.001	[14]
Dialysis	0	0	0	0	0	0	0	0	0	0	0	0	0.995	0.0995	0.005	0.0005	[17]
Transplantation	0	0	0	0	0	0	0	0	0	0	0	0	0.007	0.0007	0.993	0.0993	[17]
Standard of care (SOC)																	
From/to	CKD 1		CKD 2		CKD 3a		CKD 3b		CKD 4		CKD 5		Dialysis		Transplantation		Ref.
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	
Month 0 - 4																	
CKD 1	0.375	0.084	0.313	0.081	0.156	0.064	0.031	0.03	0.031	0.03	0.031	0.03	0.031	0.03	0.031	0.03	[14]
CKD 2	0.009	0.003	0.77	0.014	0.195	0.013	0.015	0.004	0.004	0.002	0.002	0.002	0.002	0.002	0.001	0.001	[14]
CKD 3a	0.002	0.001	0.07	0.005	0.774	0.009	0.149	0.007	0.004	0.001	0	0	0	0	0	0	[14]
CKD 3b	0.002	0.001	0.004	0.001	0.084	0.005	0.826	0.006	0.082	0.005	0.001	0.001	0.001	0	0	0	[14]
CKD 4	0.001	0.001	0.002	0.001	0.005	0.002	0.127	0.008	0.856	0.009	0.007	0.002	0.001	0.001	0.001	0.001	[14]
CKD 5	0.043	0.041	0.174	0.077	0.043	0.042	0.044	0.042	0.175	0.077	0.348	0.097	0.13	0.068	0.043	0.041	[14]
Dialysis	0	0	0	0	0	0	0	0	0	0	0	0	0.995	0.0995	0.005	0.0005	[17]
Transplantation	0	0	0	0	0	0	0	0	0	0	0	0	0.007	0.0007	0.993	0.0993	[17]
Month 5 & on																	
CKD 1	0.884	0.02	0.075	0.016	0.015	0.007	0.011	0.006	0.004	0.004	0.004	0.004	0.004	0.004	0.004	0.004	[14]
CKD 2	0.004	0.001	0.915	0.004	0.072	0.004	0.008	0.001	0.002	0.001	0	0	0	0	0	0	[14]
CKD 3a	0	0	0.023	0.001	0.91	0.003	0.064	0.002	0.003	0.001	0	0	0	0	0	0	[14]
CKD 3b	0	0	0.001	0	0.026	0.001	0.931	0.002	0.041	0.001	0	0	0.001	0	0	0	[14]
CKD 4	0	0	0.001	0	0.001	0	0.028	0.001	0.954	0.002	0.014	0.001	0.002	0	0	0	[14]
CKD 5	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.001	0.038	0.005	0.91	0.008	0.044	0.005	0.003	0.002	[14]
Dialysis	0	0	0	0	0	0	0	0	0	0	0	0	0.995	0.0995	0.005	0.0005	[17]
Transplantation	0	0	0	0	0	0	0	0	0	0	0	0	0.007	0.0007	0.993	0.0993	[17]

Table 2. Clinical and utility data included in the analysis.

	Base case	Low value	High value	Ref.
Baseline CKD				
CKD stage 2	0.105	0.08	0.13	[14]
CKD stage 3a	0.309	0.25	0.37	[14]
CKD stage 3b	0.441	0.35	0.53	[14]
CKD stage 4	0.145	0.12	0.17	[14]
Overall survival				
Dapagliflozin				
OS Weibull c	1.5893	1.2714	1.9072	[14]
OS Weibull k	0.0002	0.0001	0.0002	[14]
SOC				
OS Weibull c	1.5	1.2000	1.8000	[14]
OS Weibull k	0.002	0.0002	0.0003	[14]
Rate of adverse events				
Dapagliflozin	Base case	Low value	High value	Ref.
hHF	0.017	0.01	0.02	[10]
AKI	0.059	0.0472	0.0708	[14]
GI	0.009	0.01	0.01	[16]
UTI	0.015	0.01	0.02	[16]
Major hypoglycemia	0.007	0.0056	0.0084	[14]
SOC				
hHF	0.033	0.026	0.04	[10]
AKI	0.042	0.0336	0.0504	[14]
GI	0.001	0.001	0.001	[16]
UTI	0.016	0.013	0.019	[16]
Major hypoglycemia	0.013	0.0104	0.0156	[14]
Utilities				
CKD 1	0.85	0.68	1.02	[18]
CKD 2	0.85	0.68	1.02	[18]
CKD 3a	0.8	0.64	0.96	[18]
CKD 3b	0.8	0.64	0.96	[18]
CKD 4	0.566	0.4528	0.6792	[19]
CKD 5	0.467	0.3736	0.5604	[19]
Dialysis	0.126	0.1008	0.1512	[19]
Renal transplant	0.83	0.66	1	[20]
Disutility of AE				
hHF	0.1	0.08	0.12	[21]
AKI	0.05	0.04	0.06	[22]
GI	0.038	0.03	0.05	[22]
UTI	0.025	0.02	0.03	[22]
Severe hypoglycemia	0.01	0.008	0.012	[23]

Note: AKI: acute kidney injury; GI: genital infection; UTI: urinary tract infection; hHF: hospitalization due to HF.

Table 3. Costs included in the analysis.

	Option/dose	Base case	Low value	High value
Treatment cost	Dapagliflozin 10 mg cost per pack (28 tabs)	333	266.4	399.6
	Ramipril 2.5 mg tab cost per pack (14 tabs)	30	24.0	36.0
AE management cost	Clotrimazole cream	15	12.0	18.0
	Ciprofloxacin 250 mg tab (10 tabs)	25	20.0	30.0
	Phenazopyridine 100 mg tablet (20 tabs)	5	4.0	6.0
	Dextrose infusion	18	14.4	21.6
	Saline 9% 500 CC	18	14.4	21.6
	Glucagon 1 ml vail	90	72.0	108.0
CKD complications management	Vit D 400 IU & Ca carbonate (30 tabs)	52	41.6	62.4
	Sevelamer tablet 800 mg (30 tabs)	120	96.0	144.0
	Epoetin alfa vial	614	491.2	736.8
Hospitalization	Cost of inpatient/day (ICU room	8000	6400.0	9600.0
	Cost of inpatient/day (general ward)	2000	1600.0	2400.0
	Cost of outpatient/day	500	400.0	600.0
Transient events hHF	Isosorbide mononitrate 60 mg tablet (20 tabs)	18	14.4	21.6
	Furosemide IV (1 mL)	5.5	4.4	6.6
	Carvedilol 25 mg tablet (30 tabs)	36	28.8	43.2
Lab tests	Hb A1c	80	64.0	96.0
	Serum creatinine	25	20.0	30.0
	GFR	50	40.0	60.0
	Urea	25	20.0	30.0
	Electrolytes	45	36.0	54.0
	ACR	80	64.0	96.0
	CBC	25	20.0	30.0
	Urine protein test (24 hrs)	60	48.0	72.0
	Lipid profile	200	160.0	240.0
	LFT	200	160.0	240.0
	Upper GI endoscopy	1500	1200.0	1800.0
	Virology scan	200	160.0	240.0
	ABO typing	30	24.0	36.0
	HLA	1800	1440.0	2160.0
	Tacrolimus trough level	80	64.0	96.0
	Echocardiography	250	200.0	300.0
	X-ray	150	120.0	180.0
Dialysis	Cost of hemodialysis	2000	1600.0	2400.0
	Heparin 25,000 is (cost/IU)	15	12.0	18.0
Transplantation	Transplantation operation cost	150,000	120000.0	180000.0
	Prednisone 5 mg (20 tabs)	15	12.0	18.0
	Tacrolimus 1 mg (100 caps)	1100	880.0	1320.0
	Cyclosporin 100 mg (50 caps)	574	459.2	688.8
	Mycophenolic acid 360 mg (120 tabs)	2580	2064.0	3096.0

3.6. Sensitivity Analyses

To test the robustness of our results to variation in the estimates of the input model parameters, we performed various one-way deterministic sensitivity analyses, as recommended by Consolidated Health Economic Evaluation Reporting Standards (CHEERS): ISPOR Taskforce report [24]. All model inputs were varied through reasonable ranges/confidence intervals determined from different published sources. When standard error was not available, probability and utility were varied by ± 20%, and the cost was varied by ± 20%. The results are displayed as a tornado diagram. A probabilistic sensitivity analysis (PSA) employed the recommended distributions by Briggs *et al.* [25]. Beta distribution is appropriate for transitional probability and utility due to the range of 0 - 4. Gamma distribution is appropriate for cost data owing to the positive value. The model parameters were randomly sampled (10,000 trials) based on their distribution. The results are presented as a scatter plot on the cost-effectiveness plane.

4. Results

4.1. Base Case Result

During a lifetime horizon, the difference in cost between dapagliflozin and SOC was EGP 65,212 (USD 2126.89). The difference in QALY between dapagliflozin and SOC was 4.3.

In CKD patients, adding dapagliflozin to ramipril generates better QALYs and lower costs than ramipril alone. Dapagliflozin improved the outcomes and generated cost savings. **Table 4** shows the total results for both treatment arms in our study. Different time horizons (10 years and 20 years) were tested, and no change in the results occurred.

The progression in CKD from lower to higher CKD stages is more rapid in the SOC group than in the dapagliflozin group.

That was reflected in the segmented costs. As depicted in **Figure 2**, drug acquisition cost is higher in the dapagliflozin (46%) than in the SOC group (27%). However, dialysis costs, transplantation costs, and adverse events costs are higher in the SOC group than in the dapagliflozin group (p-value = 0.037).

4.2. Uncertainty Analyses

A deterministic one-was sensitivity analysis (**Figure 3**) revealed that the model is robust to changes in all variables included.

Table 4. Decision analysis model results.

	Difference in cost dapagliflozin-SOC	Difference in QALY dapagliflozin-SOC	ICER
10 years	−34,199	4.1	−3535
20 years	−6337	1.8	−8413
30 years (life-time)	−65,212	4.3	−15,286

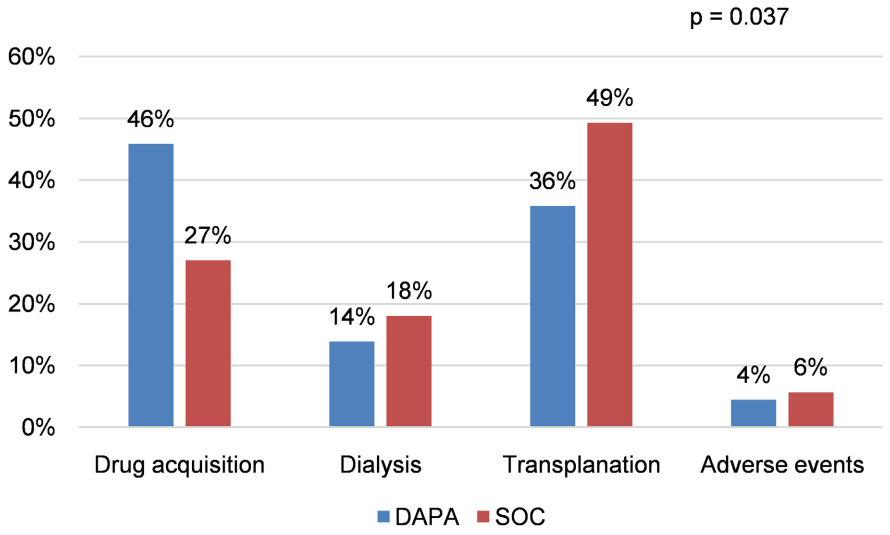


Figure 2. Percentage of different costs at life-time.

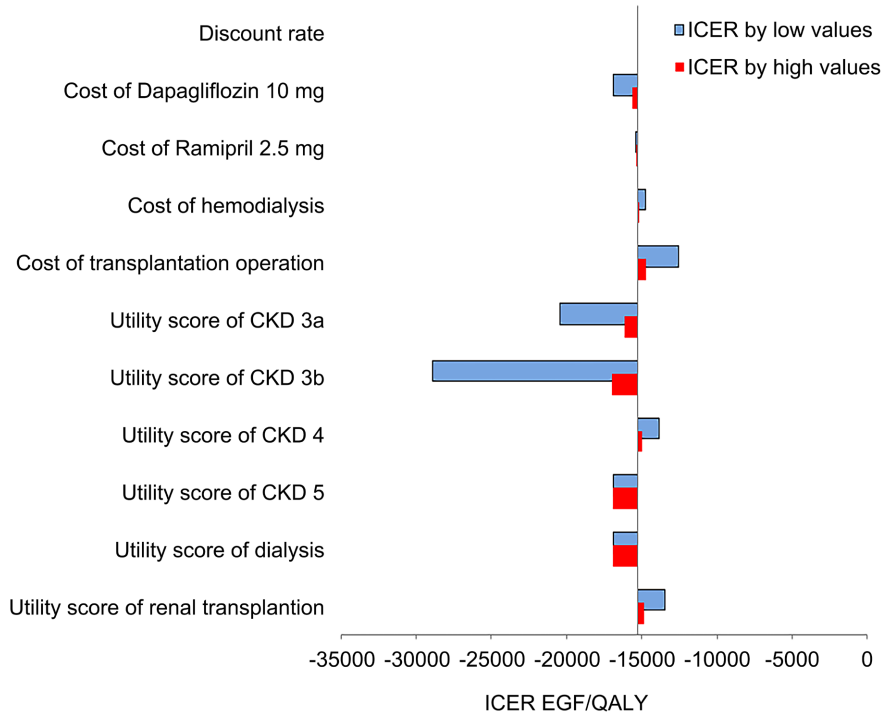


Figure 3. One-way sensitivity analyses.

PSA, using Monte Carlo simulation with 10,000 iterations, explored the effects of joint uncertainty on the model results using prespecified distributions as mentioned above. A cost-effectiveness plane was used to graphically demonstrate the variation in incremental costs and QALYs for dapagliflozin compared to SOC alone (**Figure 4**). As shown, most difference pairs are found in the northeast and southeast quadrants of the cost-effectiveness plane, which indicates that dapagliflozin use in CKD patients is more effective (positive incremental QALY scores) and that there is a large proportion in the southeast quadrant, suggest-

ing that dapagliflozin is cost saving. In about 82.64% of trials, dapagliflozin is cost-saving.

5. Impact on Budget

For patients with CKD, adding dapagliflozin by 5% led to a change in the budget by −0.6%.

On the other hand, the undertaking of dapagliflozin by 100% of them leads to a change in the budget by −11.9%, as shown in Figure 5.

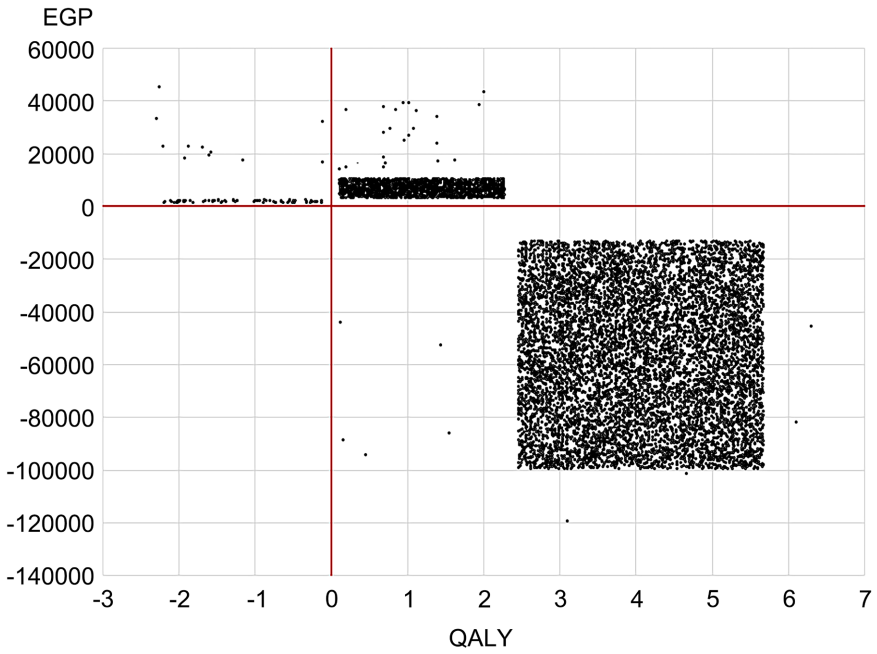


Figure 4. Cost effectiveness plane.

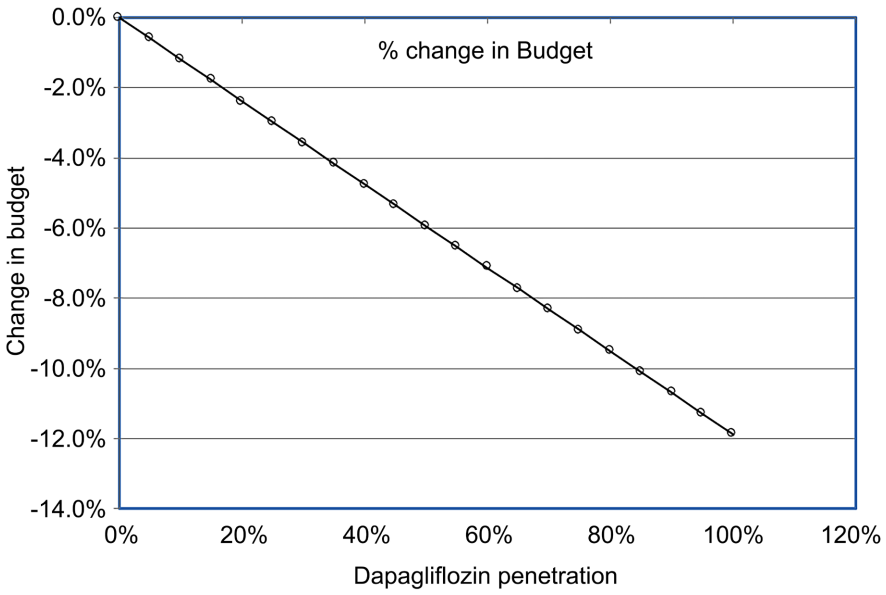


Figure 5. Change in budget by different percentages of dapagliflozin penetration.

6. Discussion

In order to address the unmet needs for CKD, new medication must be implemented. The present therapeutic alternatives, ACE and ARBs in particular, are thought to be of limited effect in delaying the progression of the illness into ESRD and have not been shown to prevent CV-related morbidity and death [15].

The principal therapeutic approach for CKD patients with ACR and eGFR values between 200 and 5000 mg/g and 25 and 75 mL/min/1.73 m^2, respectively, is dapagliflozin, which is utilized as a prophylactic against renal problems [26].

According to the findings of our study, dapagliflozin as an add-on therapy raises upfront expenses but eventually balances them out by preventing the need for dialysis or transplantation, which comes with greater monthly expenditures when compared to the early stages of CKD in Egypt compared to other countries [27].

In patients with CKD in the UK, a cost-effectiveness analysis comparing dapagliflozin as an add-on therapy to SOC over a lifetime horizon to placebo revealed that dapagliflozin was thought to be a cost-effective option in addition to improving life expectancy (LE), slowing the progression to ESRD, and lowering the likelihood of CKD adverse events (AEs), such as hHF and AKI [28].

The difference in QALYs between dapagliflozin and SOC was 4.3. The reasons why the results of our study differ from those of other studies and different countries are the local clinical practice utilized in the management of each health condition and its transitory events (resource utilization), the unit costs, and the country-specific mortality rate.

Since CKD was tenth leading cause of death globally [7], dapagliflozin's effect on lowering CV/overall mortality was not restricted to patients with a history of CVD; it was also observed in patients without a history of CV issues [29]. This indirectly improved productivity. Dapagliflozin also demonstrated a positive benefit in individuals with a baseline characteristic stage 4 that was comparable to those at stage 2/3, demonstrating consistency in the preventive effect against renal and CV endpoints throughout the advanced stages of CKD [30].

As was previously indicated, diabetes and GN were the main causes of CKD in Egypt. Since dapagliflozin regulates blood glucose levels, it can prevent the development of diabetic nephropathy (DN), a kind of chronic kidney disease [10]. According to the results of a systematic review, dapagliflozin has a nephroprotective impact against acute kidney injury (AKI) and renal mortality, in addition to lowering the incidence of ESRD among diabetes patients treated with dialysis or transplantation [31]. Moreover, dapagliflozin demonstrated a noteworthy decrease in the emergence of GN-related complications, including a 50% drop in eGFR, a lowered risk of ESRD development, and a lowered renal/CV mortality rate. Compared to 11% in the placebo group, 8% of individuals receiving dapagliflozin experienced those endpoints [32].

Due to the high expense of continuous RRT sessions and the high dialysis mortality rate, dialysis is regarded as a major burden for the developing countries like

Egypt [10]. Dapagliflozin may be able to lessen the burden of mortality in addition to all-cause mortality in patients receiving chronic dialysis [33] [34].

Egyptian people with CKD have unmet needs since the lowest quality of life is experienced by those who receive an ESRD diagnosis between six and twelve months of illness. Implementing a preventive strategy like dapagliflozin, which can decrease the progression of CKD, is therefore crucial. This will assist in managing other comorbidities, reducing the initial course of the disease, and maximizing the use of hHF resources. Over the course of a patient's lifetime, dapagliflozin has been shown to increase quality-adjusted life years (QALYs) in non-diabetic CKD patients. It also slows the progression of the disease and lowers the percentage of individuals who acquire ESRD from 17.4% to 11% [35].

There are numerous noteworthy strengths to our study. Our study's main advantage is that all of the cost parameters—which represent the payer perspective—came from Egyptian hospitals and were local. Additionally, for each cycle for both patient cohorts, our study computed the cost of transient episodes of hHF, AKI, and AEs. Additionally, we surveyed a variety of clinical specialists with varying characteristics to validate all of the model's inputs and ensure that they accurately reflected Egyptian practice. However, it is necessary to note a few restrictions. Our study modelled the economic advantages of a cohort of patients with eGFRs and ACRs ranging from 25 - 74 mL/min/1.73 m^2 and 200 - 5000 mg/g, respectively, and comparable to the one employed in DAPA-CKD. As a result, calculating the economic advantages within a cohort with distinct baseline characteristics will not be feasible. Furthermore, our study's mortality risk was taken from DAPA-CKD, which had a consistent mortality risk and a median follow-up of 2.4 years.

7. Conclusion

Because of its nephroprotective impact, dapagliflozin, independent of the aetiology of CKD, is thought to be a cost-saving choice in addition to improving QALYs in CKD patients with or without type 2 diabetes. This is due to the fact that it slows the disease's progression into end-stage renal disease (ESRD), which eventually results in a decrease in the financial burden of dialysis and transplantation on Egypt's healthcare system. During the lifetime horizon, dapagliflozin is cost-saving; it benefits the quality of life and the total cost. The addition of dapagliflozin to SOC had a saving effect of 11.9% of the budget.

Funding

AstraZeneca provided assistance with publication fees. No other funding was received for this paper.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Levin, A., Hemmelgarn, B., Culleton, B., Tobe, S., McFarlane, P., Ruzicka, M., *et al.* (2008) Guidelines for the Management of Chronic Kidney Disease. *Canadian Medical Association Journal*, **95**, 1154-1162. https://doi.org/10.1503/cmaj.080351

[2] Levey, A.S., Eckardt, K.U., Tsukamoto, Y., Levin, A., Coresh, J., Rossert, J., *et al.* (2005) Definition and Classification of Chronic Kidney Disease: A Position Statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney International*, **67**, 2089-2100. https://doi.org/10.1111/j.1523-1755.2005.00365.x

[3] Shrestha, N., Gautam, S., Mishra, S.R., Virani, S.S. and Dhungana, R.R. (2021) Burden of Chronic Kidney Disease in the General Population and High-Risk Groups in South Asia: A Systematic Review and Meta-Analysis. *PLOS ONE*, **16**, e0258494. https://doi.org/10.1371/journal.pone.0258494

[4] Lv, J.C. and Zhang, L.X. (2019) Prevalence and Disease Burden of Chronic Kidney Disease. In: Liu, B.C., Lan, H.Y. and Lv, L.L., Eds., *Renal Fibrosis: Mechanisms and Therapies*, Springer, Singapore, 3-15. https://doi.org/10.1007/978-981-13-8871-2_1

[5] Foreman, K.J., Marquez, N., Dolgert, A., *et al.* (2018) Forecasting Life Expectancy, Years of Life Lost, and All-Cause and Cause-Specific Mortality for 250 Causes of Death: Reference and Alternative Scenarios for 2016-40 for 195 Countries and Territories. *The Lancet*, **392**, 2052-2090. https://doi.org/10.1016/S0140-6736(18)31694-5

[6] GBD 2019 Diseases and Injuries Collaborators (2020) Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990-2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *The Lancet*, **396**, 1204-1222. https://doi.org/10.1016/S0140-6736(20)30925-9

[7] The Global Health Observatory of WHO (2019) Global Health Estimates: Life Expectancy and Leading Causes of Death and Disability. https://www.who.int/data/gho/data/themes/theme-details/GHO/mortality-and-global-health-estimates

[8] Nugent, R.A., Fathima, S.F., Feigl, A.B. and Chyung, D. (2011) The Burden of Chronic Kidney Disease on Developing Nations: A 21st Century Challenge in Global Health. *Nephron Clinical Practice*, **118**, c269-c277. https://doi.org/10.1159/000321382

[9] Nagib, S.N., Abdelwahab, S., El-Din Amin, G. and Allam, M.F. (2023) What Is the Prevalence of Chronic Kidney Disease among Hypertensive Non-Diabetic Egyptian Patients Attending Primary Healthcare? *Clinical and Experimental Hypertension*, **45**, Article ID: 2203411. https://doi.org/10.1080/10641963.2023.2203411

[10] El Minshawy, O. (2011) End-Stage Renal Disease in the El-Minia Governorate, upper Egypt: An Epidemiological Study. *Saudi Journal of Kidney Diseases and Transplantation*, **22**, 1048-1054.

[11] López, B., González, A., Querejeta, R., Larman, M. and Díez, J. (2012) Collagen Cross-Linking But Not Collagen Amount Associates with Elevated Filling Pressures in Hypertensive Patients with Stage C Heart Failure: Potential Role of Lysyl Oxidase. *Hypertension*, **60**, 677-683. https://doi.org/10.1161/HYPERTENSIONAHA.112.196113

[12] Heidenreich, P.A., Bozkurt, B., Aguilar, D., *et al.* (2022) 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, **79**, e263-e421. https://doi.org/10.1016/j.jacc.2021.12.012

[13] Elserafy, A.S., Reda, A., Farag, E., Mostafa, T., Farag, N., Elbahry, A., Sanad, O.,

Bendary, A., Elkersh, A., Attia, I., Selim, M., Khamis, H. and Issak, E.R. (2021) Egyptian Atherosclerosis and Vascular Biology Association Consensus on the Use of Sodium Glucose Cotransporter-2 Inhibitors in Heart Failure with Reduced Ejection Fraction. *Clinical Drug Investigation*, **41**, 1027-1036. https://doi.org/10.1007/s40261-021-01095-6

[14] Heerspink, H., Stef Ansson, B.V., Correa-Rotter, R., *et al.* (2020) Dapagliflozin in Patients with Chronic Kidney Disease. *The New England Journal of Medicine*, **383**, 1436-1446. https://doi.org/10.1056/NEJMoa2024816

[15] National Institute for Health and Care Excellence (NICE) (2022) Dapagliflozin for Treating Chronic Kidney Disease. https://www.nice.org.uk/guidance/ta775/resources/dapagliflozin-for-treating-chronic-kidney-disease pdf-82611498049477

[16] McMurray, J., Wheeler, D.C., Stefansson, B.V., *et al.* (2021) Effects of Dapagliflozin in Patients with Kidney Disease, with and without Heart Failure. *JACC*: *Heart Failure*, **9**, 807-820. https://doi.org/10.1016/j.jchf.2021.06.017

[17] Sugrue, D.M., Ward, T., Rai, S., McEwan, P. and van Haalen, H.G.M. (2019) Economic Modelling of Chronic Kidney Disease: A Systematic Literature Review to Inform Conceptual Model Design. *PharmacoEconomics*, **37**, 1451-1468. https://doi.org/10.1007/s40273-019-00835-z

[18] Jesky, M.D., Dutton, M., Dasgupta, I., *et al.* (2016) Health-Related Quality of Life Impacts Mortality But Not Progression to End-Stage Renal Disease in Pre-Dialysis Chronic Kidney Disease: A Prospective Observational Study. *PLOS ONE*, **11**, e0165675. https://doi.org/10.1371/journal.pone.0165675

[19] Kularatna, S., Senanayake, S., Gunawardena, N. and Graves, N. (2019) Comparison of the EQ-5D 3L and the SF-6D (SF-36) Contemporaneous Utility Scores in Patients with Chronic Kidney Disease in Sri Lanka: A Cross-Sectional Survey. *BMJ Open*, **9**, e024854. https://doi.org/10.1136/bmjopen-2018-024854

[20] Li, B., Cairns, J.A., Draper, H., *et al.* (2017) Estimating Health-State Utility Values in Kidney Transplant Recipients and Waiting-List Patients Using the EQ-5D-5L. *Value Health*, **20**, 976-984. https://doi.org/10.1016/j.jval.2017.01.011

[21] Bertoldi, E.G., Rohde, L.E., Zimerman, L.I., *et al.* (2013) Cost-Effectiveness of Cardiac Resynchronization Therapy in Patients with Heart Failure: The Perspective of a Middle-Income Country's Public Health System. *International Journal of Cardiology*, **163**, 309-315. https://doi.org/10.1016/j.ijcard.2011.06.046

[22] McEwan, P., Darlington, O., McMurray, J.J.V., Jhund, P.S., Docherty, K.F., B€ohm, M., Petrie, M.C., Bergenheim, K. and Qin, L. (2020) 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**, 2147-2156. https://doi.org/10.1002/ejhf.1978

[23] Beaudet, A., Clegg, J., Thuresson, P.O., Lloyd, A. and McEwan, P. (2014) Review of Utility Values for Economic Modeling in Type 2 Diabetes. *Value Health*, **17**, 462-470. https://doi.org/10.1016/j.jval.2014.03.003

[24] Husereau, D., Drummond, M., Petrou, S., *et al.* (2013) Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health*, **16**, 231-250. ttps://doi.org/10.1016/j.jval.2013.02.002

[25] Briggs, A. and Sculpher, M. (1998) An Introduction to Markov Modelling for Economic Evaluation. *PharmacoEconomics*, **13**, 397-409.

https://doi.org/10.2165/00019053-199813040-00003

[26] HAS (2020) Committee Meeting of Dapagliflozin FORXIGA 10 mg Filmcoated Tablets. https://www.has-sante.fr/upload/docs/application/pdf/2021-03/forxiga_18112020_summary_ct18815.pdf

[27] Vareesangthip, K., Deerochanawong, C., Thongsuk, D., Pojchaijongdee, N. and Permsuwan, U. (2022) Cost-Utility Analysis of Dapagliflozin as an Add-on to Standard of Care for Patients with Chronic Kidney Disease in Thailand. *Advances in Therapy*, **39**, 1279-1292. https://doi.org/10.1007/s12325-021-02037-6

[28] McEwan, P., Darlington, O., Wheeler, D., *et al.* (2022) POS-335 Cost-Effectiveness of Dapagliflozin as a Treatment for Chronic Kidney Disease: A Health-Economic Analysis of DAPA-CKD. *Clinical Journal of the American Society of Nephrology*, **17**, 1730-1741. https://doi.org/10.2215/CJN.03790322

[29] McMurray, J.J.V., Wheeler, D.C., Stefansson, B.V., *et al.* (2021) Effect of Dapagliflozin on Clinical Outcomes in Patients with Chronic Kidney Disease, with and without Cardiovascular Disease. *Circulation*, **143**, 438-448. https://doi.org/10.1161/CIRCULATIONAHA.120.051675

[30] Chertow, G.M., Vart, P., Jongs, N., *et al.* (2021) Effects of Dapagliflozin in Stage 4 Chronic Kidney Disease. *Journal of the American Society of Nephrology*, **32**, 2352-2361. https://doi.org/10.1681/ASN.2021020167

[31] Neuen, B.L., Young, T., Heerspink, H.J.L., *et al.* (2019) SGLT2 Inhibitors for the Prevention of Kidney Failure in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *The Lancet Diabetes and Endocrinology*, **7**, 845-854. https://doi.org/10.1016/S2213-8587(19)30256-6

[32] Wheeler, D.C., Jongs, N., Stefansson, B.V., *et al.* (2022) Safety and Efficacy of Dapagliflozin in Patients with Focal Segmental Glomerulosclerosis: A Prespecified Analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) Trial. *Nephrology Dialysis Transplantation*, **37**, 1647-1656. https://doi.org/10.1093/ndt/gfab335

[33] AlSahow, A. and AlYousef, A. (2021) Global Dialysis Perspective: Kuwait. *Kidney* 360, **2**, 1015-1020. https://doi.org/10.34067/KID.0000392021

[34] Heerspink, H.J.L., Sj€ostr€om, C.D., Jongs, N., *et al.* (2021) Effects of Dapagliflozin on Mortality in Patients with Chronic Kidney Disease: A Prespecified Analysis from the DAPA-CKD Randomized Controlled Trial. *European Heart Journal*, **42**, 1216-1227. https://doi.org/10.1093/eurheartj/ehab094

[35] Tisdale, R.L., Cusick, M.M., Aluri, K.Z., *et al.* (2022) Cost-Effectiveness of Dapagliflozin for Non-Diabetic Chronic Kidney Disease. *Journal of General Internal Medicine*, **37**, 3380-3387. https://doi.org/10.1007/s11606-021-07311-5