Cost-effectiveness analysis of empagliflozin for adults with Chronic Kidney Disease (CKD) in Greece

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Objective

To demonstrate the cost-effectiveness of empagliflozin + Standard of care (SoC) versus SoC alone for the management of adult patients with Chronic Kidney Disease (CKD) in Greece.

Introduction

- CKD, defined by abnormalities in kidney structure or function lasting over 3 months with adverse health outcomes, is classified based on cause, glomerular filtration rate (GFR) category, and albuminuria category (referred to as "CGA" staging), where estimated GFR (eGFR) indicates kidney function and albuminuria reflects glomerular damage[1].
- Research shows low CKD awareness worldwide, leading to late-stage diagnoses and reduced treatment options, while approximately 8,236 per 100,000 individuals with CKD remain undiagnosed in Greece, reflecting a 3.7% increase over a five-year time horizon [2-5].
- In Greece, the prevalence of CKD was higher than 10% (NHANES survey), given that Greece has one of the older populations in Europe[6].
- Until recently, treatment options to slow CKD progression were limited to angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), statins, and antiplatelets, which primarily slow disease progression without halting it. However, recent advances have introduced sodium-glucose transport protein 2 (SGLT-2) inhibitors, such as dapagliflozin, canagliflozin, and empagliflozin, which have been shown to reduce risks associated with CKD, including sustained eGFR decline, end-stage kidney disease (ESKD), cardiovascular death, and hospitalizations for heart failure[7].
- Empagliflozin led to a lower risk of progression of kidney disease and lesser deaths from cardiovascular causes in CKD patients[8]. Based on the results of the EMPA-KIDNEY trial[9-11], an once-daily empagliflozin significantly decreased the risk of CKD progression and cardiovascular death to 13.1% compared to 16.9% with placebo, while evaluating the drug's safety across a broad range of CKD patients.

Model structure

- A Markov state microsimulation model was developed to estimate the total lifetime cost per patient, life years (LYs) and quality-adjusted life-years (QALYs) for each arm of the analysis, as well as the incremental cost-effectiveness ratio (ICER) per LY and QALY gained, respectively, from the perspective of public payer in Greece.
- An 3.5% annual discount rate for both costs and QALYs was used in the analysis.
- In the model, health states are defined by Kidney Disease: Improving Global Outcomes (KDIGO) classification, with complications risk varying based on eGFR, Urine albumin-creatinine ratio (uACR), diabetes, hypertension, age, lipid levels, and systolic blood pressure, and all fatal cases are classified under "all-cause death".
- The progression of eGFR and uACR over time and their impact on the risk of developing events and complications were retrieved from public literature (Grams et al. 2020[12], Coresh et al. 2019[13]).
- Patients can die at any time during the modeled lifetime due to non-specific mortality, cardiovascular death, or renal death, with non-specific mortality rates derived from World Health Organization (WHO) National Life Tables for Greece[14] by excluding CVD and renal causes, while cardiovascular mortality probabilities were calculated using the proportion of cardiovascular deaths (ICD-10: I20-I25 and I60-I69) from total deaths based on Hellenic Statistical Authority data (EL. STAT.)[15].

Patient population and treatment options

- The patient population of interest were adults (age 18 years and older) who had CKD, defined as an eGFR <90 ml/min per 1.73 m^2.
- In Greece, SoC such as Angiotensin-converting enzyme ACEi, ARBs, statins and antiplatelets persists the most marketed treatment path, based on local clinical experts' opinion.
- Drug utilisation of each category was based on local clinical experts' estimates (**Table 1**).

Table 1. SoC drug classes, drug acquisition dosing scheme and unit cost (€, 2023)

Treatment Class	SoC Utilisation[1]	Drug	Pack Size	Strength (mg)	Cost/ Pack size[2]	Daily dose (mg)
SGLT2 Inhibitor		Empagliflozin	30	10	€ 47.96	10
		Dapagliflozin	28	10	€ 44.17	10
ACEi	16%	Ramipril	20	5	€ 4.54	10
		Perindopril	30	10	€ 3.00	10
		Lisinopril	28	20	€ 4.83	20
ARBs	74%	Irbesartan	28	300	€ 5.48	300
		Losartan	28	50	€ 2.70	100
		Valsartan	14	320	€ 2.74	320
		Olmesartan	28	40	€ 5.42	40
		Azilsartan	28	80	€ 4.64	80
		Candesartan	14	32	€ 2.74	32
Statins	85%	Atorvastatin	14	40	€ 3.69	40
		Rosuvastatin	14	40	€ 3.69	40
		Pitavastatin	30	4	€ 12.21	4
Antiplatelets	85%	Aspirin	30	100	€ 1.72	100
		Clopidogrel	28	75	€ 8.31	75
CCBs	32.5%	Amlodipine	30	10	€ 7.41	10
Diuretics	22.5%	Hydrochlorothiazide	20	25	€ 1.12	25

Source: [1] Drug utilisation based on local clinical experts' estimates. [2] Positive list for the reimbursement of medicines[16]

Data analysis

- The cost effectiveness of empagliflozin + SoC versus SoC was evaluated by calculating the incremental cost per QALY gained.
- A discount rate of 3.5% for cost and health outcomes.
- One-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis were undertaken to test the robustness of the base-case findings.

Costs

- Healthcare resource use and cost inputs relating to drug acquisition, disease management, events and complications and adverse event costs were considered in the model.
- The drug acquisition costs were calculated by combining the drug doses and frequency of administration, as provided by local clinical experts, with the reimbursed drugs unit costs, following current legislation and publicly available price data (**Table 1**).
- Costs of events and complications and adverse event costs were obtained from the literature (**Table 2**).
- The annual cost per patient was estimated by KDIGO class (stage 2-3b, stage 4 and stage 5 {pre-dialysis}) (**Table 3**).

Table 2. Costs of adverse events and complications

Events and complications		
Acute costs		
CVD co-morbidities and complications	**Costs**	**Sources**
Myocardial infarction	€ 5,829	Gourzoulidis et al. 2018[17]
Unstable angina	€ 3,510	
Stroke (including transient ischemic attack)	€ 4,281	
Congestive heart failure (hospitalizations)	€ 3,799	
Transient ischemic attack	€ 1,061	Andrikopoulos et al. 2013[18]
Peripheral arterial and vascular disease (driven by smoking, stenting)	€ 5,269	Tzanetakos et al. 2014[19]
End Stage Renal disease and events	**Costs**	**Sources**
Conservative Therapy	€ 2,970	Local clinical experts' estimates
Continuous ambulatory peritoneal dialysis*	€ 1,592	
Automated peritoneal dialysis**	€ 2,989	
Hemodialysis	€ 37,218	Tzanetakos et al. 2014[19]
Kidney transplant (living donor)	€ 17,053	
Kidney transplant (deceased donor)	€ 17,053	
Acute kidney injury - hospitalization	€ 725	Gourzoulidis et al. 2018[17]
Peritonitis	€ 3,087	
AV access thrombosis	€ 415	Local clinical experts' estimates
Bloodstream infections	€ 156	
Metabolic and mineral disorder	**Costs**	**Sources**
Metabolic acidosis	€ 254	Local clinical experts' estimates
Hyperkalemia	€ 678	
Hyperphosphatemia	€ 322	
Secondary hyperparathyroidism	€ 185	Data on file
Hyperuricemia/Gout	€ 114	Local clinical experts' estimates
Hypocalcemia	€ 295	Terpos et al. 2019[20]
Bone and skeleton disorders	**Costs**	**Sources**
Hip fractures	€ 710	Local clinical experts' estimates
Other fractures	€ 34	
Infections	**Cost**	**Sources**
Respiratory infections	€ 156	Local clinical experts' estimates
Urinary track infection	€ 49	
Skin and soft tissue infections	€ 84	
Gastrointestinal infection	€ 39	
Muscular infections	€ 13	
Nervous system	€ 13	
Sepsis	€ 2,230	Loupas et al. 2022[21]
Anemia	€ 242	
Cancer	**Costs**	**Sources**
Renal cancer	€ 1,629	Local clinical experts' estiimates
Urothelial cancer	€ 346	
All cause hospitalization	**Costs**	**Sources**
All cause hospitalization	€ 2,323	Diagnostic Related Groups (DRGs)
Follow-up (after first year) Hospitalization Costs		
CVD co-morbidities and complications	**Costs**	**Sources**
Myocardial infarction	€ 1,109	Tzanetakos et al. 2016[22]
Unstable angina	€ 1,820	
Stroke (including transient ischemic attack)	€ 1,831	
Congestive heart failure (hospitalizations)	€ 1,295	
Transient ischemic attack	€ 188	Local clinical experts' estimates
Peripheral arterial and vascular disease	€ 1,315	
End Stage Renal disease and events	**Costs**	**Sources**
Immunosuppressive Therapy for kidney transplantation	€ 4,981	Tzanetakos et al. 2014[19]
Adverse Events Costs		
Lower limb amputation	**Costs**	**Sources**
Leg amputation	€ 79	Local clinical experts' estimates
Toe amputation	€ 35	
Foot amputation	€ 40	

Notes: *4% patients on CAPD; **5% patients on APD

Table 3. Disease Management Costs per Health State as per KDIGO classification

Health State as per KDIGO classification	Annual Costs
G+90_A-30	€ 944
G+90_A-300	€ 1,183
G+90_A+300	€ 1,543
G+60_A-30	€ 944
G+60_A-300	€ 1,183
G+60_A+300	€ 1,543
G+45_A-30	€ 971
G+45_A-300	€ 1,148
G+45_A+300	€ 1,511
G+30_A-30	€ 1,122
G+30_A-300	€ 1,325
G+30_A+300	€ 1,836
G+15_A-30	€ 1,407
G+15_A-300	€ 1,650
G+15_A+300	€ 2,218
G-15_A-30	€ 1,590
G-15_A-300	€ 1,945
G-15_A+300	€ 3,661

Results

- Over a lifetime horizon, the addition of empagliflozin to SoC resulted in an extra cost of €246 per patient compared to SoC alone, largely due to empagliflozin's acquisition cost per patient.
- This additional cost was partially offset by a €6,224 reduction in kidney replacement therapy costs per patient with empagliflozin plus SoC, compared to SoC alone.
- Patients in the empagliflozin arm had better survival outcomes, leading to slightly higher costs for monitoring and other CKD complications, with the incremental analysis showing an ICER of €256 per QALY gained and €197 per LY gained (**Table 4**).
- Results of OWSA and PsA confirmed the robustness of base case, highlighting the cost-effective profile of empagliflozin + SoC versus SoC alone.

Table 4. SoC drug classes, drug acquisition dosing scheme and unit cost (€, 2023)

Outcomes	Empagliflozin+ SoC	SoC	Incremental
Total costs per patient	€ 61,944.15	€ 61,697.98	€ 246.16
Total QALYs per patient	6.99	6.03	0.962
Total LYs per patient	9.43	8.18	1.247
	ICER per QALY gained		€255.92
	ICER per LY gained		€197.37

Conclusion

Empagliflozin added to SoC was estimated to be a highly cost-effective treatment option for the treatment of adults with CKD compared to Soc in Greece.

Abbreviations
ACEi, angiotensin-converting enzyme. inhibitors; ARBs, angiotensin-receptor blockers; CCBs, Calcium channel blockers; CGA, Cause, GFR category and albuminuria category; CKD, Chronic Kidney Disease; EGFR, estimated GFR; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; ICER, incremental cost-effectiveness ratio; KDIGO, Kidney Disease: Improving Global Outcomes; LYs, life years; OWSA, One-way sensitivity analysis; QALYs, quality-adjusted life-years; SGLT-2, sodium-glucose transport protein 2; SoC, Standard of care

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