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Budget Impact Analysis of Expanding Gliflozin Coverage in the CKD Population: A French Perspective

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ABSTRACT

Introduction: Gliflozins have historically been indicated for type 2 diabetes in France. However, their efficacy has recently been demonstrated in heart failure and chronic kidney disease (CKD), with positive recommendations by Haute Autorité de Santé for gliflozin therapies in these indications. The study objective was to investigate the 5-year budget impact

associated with the introduction of gliflozins in addition to standard therapy in people with CKD and elevated albuminuria, regardless of diabetes status, from the perspective of the French healthcare system.

Methods: A budget impact model was developed to estimate the 5-year implications of incorporating gliflozins in the treatment of patients with CKD in France, using efficacy data

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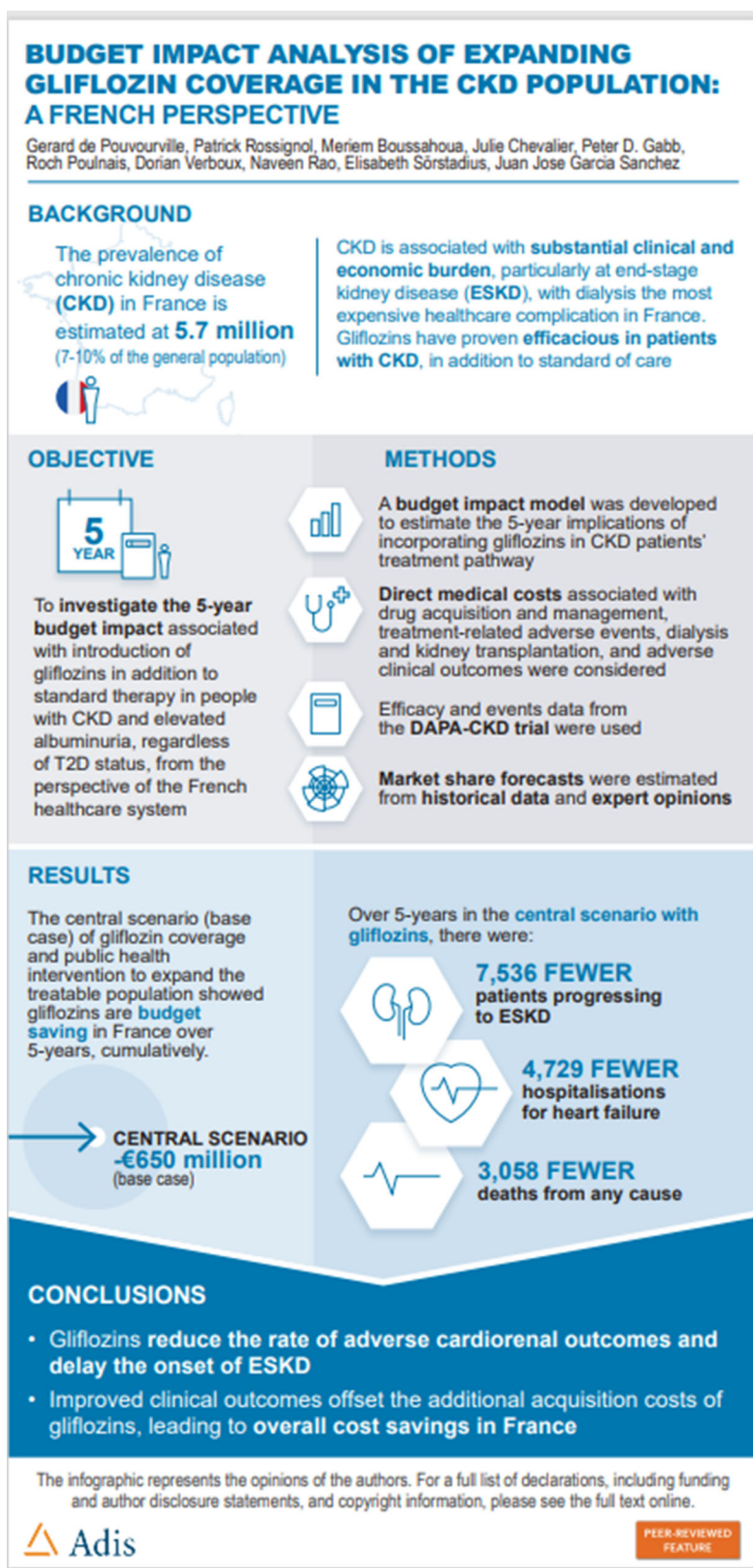
from the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial. Direct medical costs associated with drug acquisition and management, treatment-related adverse events, dialysis and kidney transplantation, and adverse clinical outcomes were considered. Market share forecasts were estimated from historical data and expert opinions. Event rates were derived from trial data, while cost data were sourced from published estimates.

Results: The introduction of gliflozins was estimated to be cost saving compared to the no gliflozins scenario, with an expected cumulative 5-year budget impact of -€650 million, driven by slowed disease progression in patients treated with gliflozins, with fewer patients cumulatively progressing to end-stage kidney disease

(84,526 vs. 92,062). This, in addition to fewer hospitalisations for heart failure and deaths from any cause, led to substantial medical care cost offsets (kidney-related: -€894 million; hospitalisation for heart failure: -€14.3 million; end-of-life care: -€17.3 million) to the additional drug acquisition (€273 million) and treatment-related adverse events costs (€2.98 million).

Conclusion: In concert with early diagnosis and proactive management of CKD, the expansion of the gliflozin indications into the French CKD population presents the opportunity to reduce the substantial burden associated with cardio-renal complications which outweighs the additional cost of the new treatment.

Infographic:



Keywords: Chronic kidney disease; Budget impact analysis; SGLT2 inhibitors; End-stage kidney disease

DIGITAL FEATURE

This article is published with digital features, including an infographic, to facilitate understanding of the article. To view digital features for this article go to: <https://doi.org/10.6084/m9.figshare.23183681>.

Key Summary Points

The introduction of gliflozins as a treatment option for patients with chronic kidney disease (CKD) is predicted to lead to a reduction in the number of patients incurring cardio-renal complications.

A projected reduction in numbers of patients undergoing dialysis or transplantation is expected to lead to a large reduction in associated costs.

A reduction of adverse clinical outcomes leads to estimated cost offsets compared to additional drug acquisition and treatment-related adverse event costs, such that the introduction of gliflozins is predicted to be particularly cost saving over a 5-year period (– €650 million; eligible CKD population at year 5: 641,746), increasing substantially in a scenario analysis of greater public health intervention (– €1.53 billion; eligible CKD population at year 5: 754,748).

Overall annual costs per patient treated with gliflozins were expected to be lower compared to those treated with standard therapy alone; considerable healthcare expenditure spent addressing cardio-renal complications can be avoided through an increased rate of diagnosis and enrolment of patients on treatments for CKD.

INTRODUCTION

In France, the prevalence of adults with chronic kidney disease (CKD), defined as urine albumin–creatinine ratio (UACR) > 30 mg/g or estimated glomerular filtration (eGFR) < 60 ml/min per 1.73 m², is estimated at 5.7 million, or 7–10% of the general population [1, 2]. CKD is associated with substantial clinical and economic burden, with CKD progression ultimately leading to end-stage kidney disease (ESKD), where the burden of cardio-renal complications becomes most significant for patients and healthcare systems [3, 4]. According to the REIN (Réseau Épidémiologie et Information en Néphrologie) national report for 2019, approximately 92,000 people suffer from ESKD in France [5]. Mortality rates in these patients are high, with a 10-year mortality of 49% according to the same report [5]. This translates into a substantial economic burden: according to the annual Court of Auditors report, ESKD is the most expensive pathology in France [6], with an annual cost of €78,492 per dialysis patient [7], leading to more than €4 billion expenditure per year at the national level.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines stratify CKD according to eGFR (stages G1–5) and UACR (stages A1–3) [8, 9]. Patients in stages G1 and G2 are typically asymptomatic [10], and CKD burden is further exacerbated by failure or delay in diagnosis; according to a recent study, only 10% of stage G3 patients are identified [11]. As a result, many patients start receiving treatments when the disease is already in advanced stages and in need of costly interventions. Indeed, over 30% of patients with ESKD are urgently placed on dialysis in France [12], and it is estimated that 18% and 4% of patients initiated on haemodialysis and peritoneal dialysis, respectively, have not had a prior nephrological consultation [13].

Renin–angiotensin–aldosterone system inhibitors (RAASi), including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), are considered to be the most effective proven treatment option in

the management of CKD and currently constitute the standard of care in France [14]. Nevertheless, the condition continues to advance quickly for some patients despite treatment, and the residual risk of kidney failure, cardiovascular complications and premature death remains high [14–16].

Gliflozins [or sodium-glucose transport protein 2 (SGLT2) inhibitors]—specifically canagliflozin, dapagliflozin and empagliflozin—are established treatments for type 2 diabetes (T2D). They have also proven efficacious in patients with heart failure [17, 18] and CKD in addition to standard of care [19–21]. The latest American Diabetes Association 2022 guidelines included a grade A recommendation to use gliflozins for patients with T2D and diabetic kidney disease with an eGFR ≥ 25 mL/min per 1.73 m^2 and UACR ≥ 300 mg/g, to reduce CKD progression and cardiovascular events [22]. Similarly, KDIGO 2022 guidelines for diabetes management in CKD position gliflozins as first-line therapeutics [23, 24], with updated guidance on CKD management in patients without T2D expected to follow.

The landmark Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial was terminated early due to overwhelming efficacy, demonstrating for the first time the value of gliflozins in patients with CKD regardless of T2D status [25]. In the trial, dapagliflozin showed statistically significant reductions in the primary composite endpoint, defined as $\geq 50\%$ sustained decline in eGFR, onset of ESKD, or cardiovascular/kidney-related death, [hazard ratio (HR) 0.61; 95% confidence interval (CI) 0.51–0.72; $P < 0.001$], hospitalisations for heart failure or cardiovascular death (HR, 0.71; 95% CI 0.55–0.92; $P = 0.009$) and death from any cause (HR, 0.69; 95% CI 0.53–0.88; $P = 0.004$).

Similarly, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial has recently demonstrated the clinical benefits of this class of drugs in patients with both T2D and CKD [26], while the EMPA-KIDNEY study, which investigated the effects of empagliflozin in CKD, was also stopped early due to reduced progression of kidney disease and death from

cardiovascular causes [19]. Despite the large body of evidence supporting gliflozins' efficacy in CKD, dapagliflozin remains the only therapy reimbursed in France for patients with CKD (with/without T2D), although other options are under review or are likely to be reviewed in the future.

The emergence of gliflozins as an option for patients is likely to cause a notable shift in patient outcomes and healthcare service utilisation in the coming years. Indeed, it is possible to speculate that early initiation of gliflozin-based therapy may positively influence both patients and healthcare providers, due to slowed disease progression to kidney failure and reduced adverse cardio-renal outcomes, leading to significant expected medical care cost offsets. The economic value of gliflozins has been previously assessed in other settings [27]; however, there is a paucity of published budget impact analyses assessing CKD treatments, particularly from the French perspective.

Therefore, the primary objective of this study is to develop a budget impact analysis to assess the effect of an increase in the number of patients screened and treated for CKD with gliflozins compared to standard therapy alone. The study assesses the impact of improving CKD diagnosis and management via the implementation of public health interventions over a 5-year period, with an additional scenario analysis extended to 10 years, from the perspective of the French national health insurance.

METHODS

Model Structure

This budget impact analysis of gliflozin therapies considers the perspective of the mandatory French national health insurance, l'Assurance Maladie Obligatoire (AMO), and is based on the structure of the model validated by the French health technology assessment authority, Haute Autorité de Santé (HAS) [7]. Direct costs (drug acquisition, renal, cardiovascular, and treatment-related adverse events) were incorporated; indirect costs, such as productivity loss, were

excluded. The central scenario (base case) analysis utilises a short-term 5-year time horizon in line with common practice and guidance [28, 29]. A schematic of the model used to estimate the effect of public health interventions is outlined in Fig. 1.

We used an event-driven budget impact model (Fig. 2) to estimate the rate of clinical events and associated direct medical costs under two alternative situations: “world without gliflozins” reflecting the current mix of therapies defined as standard therapy; “world with gliflozins” reflecting the addition of gliflozins to a standard therapy in CKD treatment regimens.

Eligible Population

At the time of this analysis, dapagliflozin is the only publicly reimbursed gliflozin therapy in

France in this indication. The eligible population for this analysis therefore corresponds to the selection criteria of the DAPA-CKD trial. Specifically, this analysis is relevant to adult patients with eGFR ≥ 25 mL/min per 1.73 m^2 and ≤ 75 mL/min per 1.73 m^2 , and UACR ≥ 200 mg/g and ≤ 5000 mg/g, treated with RAASi therapy at the maximum tolerated dose for at least 4 weeks.

According to HAS, the prevalence of patients with UACR > 30 mg/g and/or eGFR < 60 ml/min per 1.73 m^2 is 3 million [2], of which an estimated 73% would be diagnosed, according to a qualitative panel of nephrologists. To translate the DAPA-CKD population to the French national setting, the French CKD-REIN cohort, which showed that 33% of patients with CKD have a urine albumin-creatinine ratio between 200 and 5000 mg/g [30], was used to extrapolate to 722,700 patients in the national

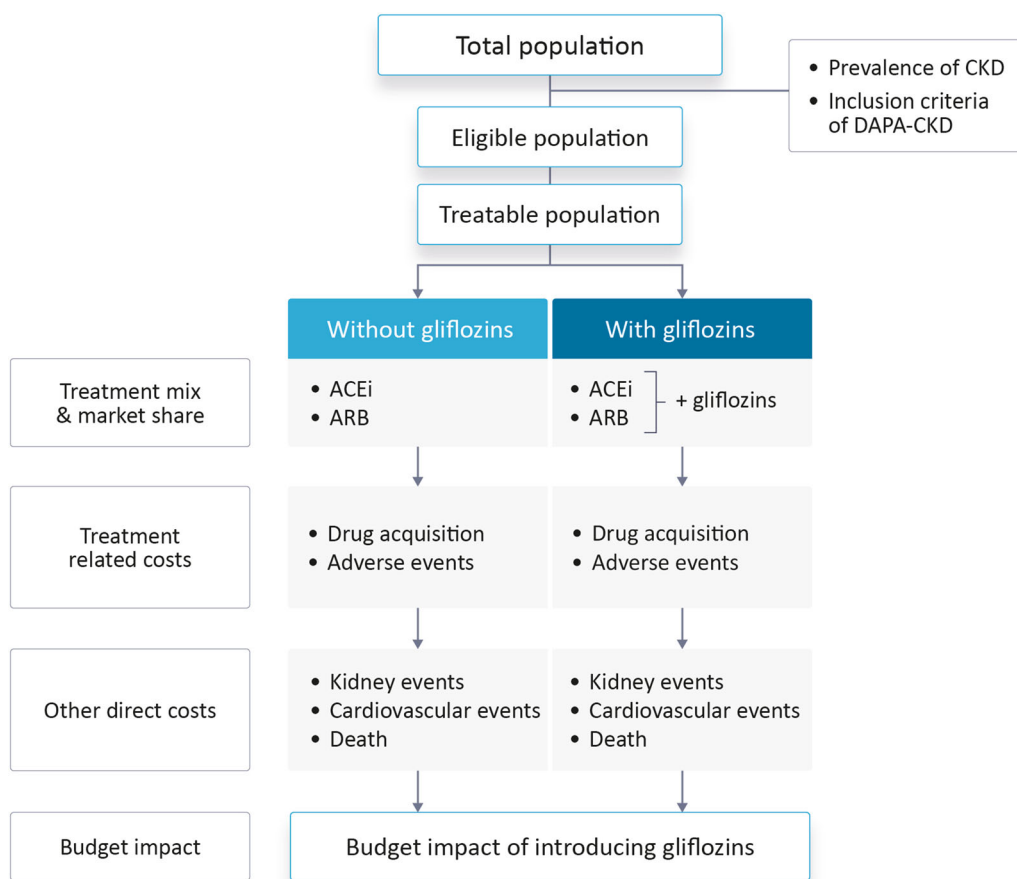


Fig. 1 Schematic of the budget impact analytical framework. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *DAPA-CKD* Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease

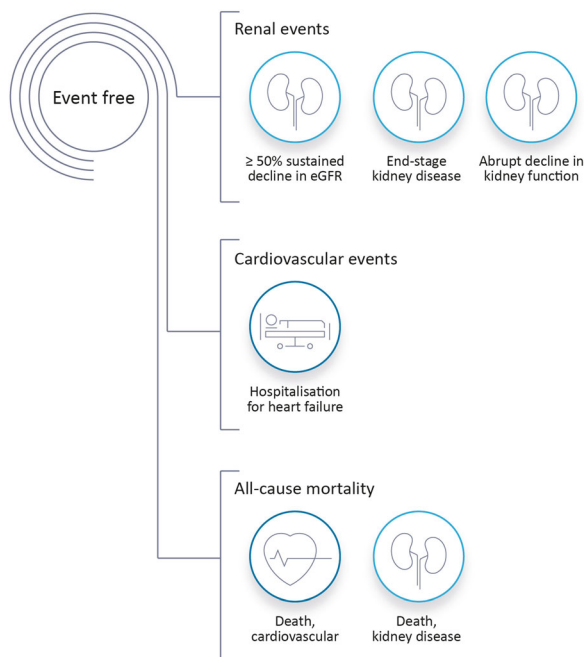


Fig. 2 Events considered in the budget impact analysis of the introduction of gliflozins into the CKD treatment pathway. *eGFR* estimated glomerular filtration rate

adult population. In addition, a qualitative panel of nephrologists estimated that 25% of adults living with CKD are not receiving RAASi treatment. Of those receiving treatment, the proportion receiving ACE inhibitors or ARBs cannot be estimated with precision. Therefore, by estimating that RAASi is suboptimal in 30% patients, we estimate that approximately 379,000 individuals with CKD would be eligible for dapagliflozin in the national adult population in the first year [7].

The “central scenario” (base case) forecasts an increase in patients diagnosed and treated due to the implementation of public health interventions, increasing the eligible population by approximately 70% by year 5; alternative scenarios of public health intervention are also explored.

Healthcare Interventions

The scenario representing standard therapy was defined as a mix of RAASi therapies; specifically, either ACEi or ARB in line with current clinical

practice in France and as standard therapy was defined in the DAPA-CKD trial. The proportion of patients receiving ACEi or ARB is determined throughout the model according to market share forecasts and is assumed to be constant over the modelled period (ACEi: 50.9%; ARB: 49.1%). The introduction of gliflozins scenario assumes that gliflozin therapies will be used in addition to RAASi, and that its introduction will not impact the composition of background therapies. Therefore, market share changes are applied equally to prevalent and incident patients with CKD.

The eligible population in France is expected to increase over time, mainly due to the ageing of the population based on projections by the National Institute of Statistics and Economic Studies (Institut National de la Statistique et des Études Économiques) [31], in addition to an increasing prevalence of T2D according to the International Diabetes Federation [32]. However, the treatable diagnosed population will increase most significantly through implementing national public health interventions with the purpose of reducing the proportion of undiagnosed people living with CKD. This could, in turn, lead to improved health outcomes in this population.

Clinical Efficacy Data

The efficacy data used to estimate health outcomes for gliflozin therapy in the eligible population were derived from patient data from the DAPA-CKD trial; annual probabilities are stated in Table 1. Accordingly, kidney events considered in the model include $\geq 50\%$ sustained decline in eGFR, reaching ESKD (with patients assumed to progress either to dialysis or transplant), in addition to abrupt decline in kidney function (predefined end point of doubling of serum creatinine between two visits as a result of acute intermittent events). The model also incorporates hospitalisation for heart failure. Modelled death was defined as death from any cause (all-cause mortality). Treatment-related adverse events considered in the model include volume depletion, major hypoglycaemic

Table 1 Clinical event rates

Events	Gliфлоzin plus standard therapy	Standard therapy
Clinical events, per 100 patient years		
≥ 50% sustained decline in eGFR	2.6	4.8
End-stage kidney disease ^a	2.5	3.8
Hospitalisation for heart failure	0.8	1.6
Abrupt decline in kidney function	1.4	2.0
All-cause mortality	2.2	3.1
Treatment-related adverse events, per 100 patient years		
Volume depletion	0.0016	0.0025
Major hypoglycaemic event	0.0019	0.0027
Fracture	0.0041	0.0025
Diabetic ketoacidosis	0.0000	0.0002
Amputation	0.0054	0.0046

eGFR estimated glomerular filtration rate

^aRates are applied only to patients without ESKD

events, fractures, diabetic ketoacidosis and amputation.

Cost and Healthcare Resource Use

Costs incorporated are direct costs only, comprised of drug acquisition and treatment-specific disease management costs, kidney- and cardiovascular-related event management costs, adverse-event-related costs, end-of-life costs, and transport costs. In France, the long-term diseases scheme allows complete reimbursement from the AMO of healthcare expenditures for individuals with specific conditions such as T2D and CKD. Thus, direct costs are assumed to be entirely covered by this scheme. Costs are

estimated according to French national health insurance prices at the full public price.

The annual drug acquisition cost of any gliflozin therapy was assumed to be the cost of dapagliflozin (€484) based on health insurance tariffs [33], and were calculated from the doses of the treatments administered, unit costs and the frequency of administration. Based on expert opinion of prescribing practices, standard therapy (ACEi/ARB) was derived from acquisition costs for irbesartan, losartan and ramipril, which were, respectively, the lowest cost per drug class and were equal in value. Treatment specific disease management costs included follow-up consultations, tests, and medical procedures.

Following discontinuation of dapagliflozin, it was assumed that patients incurred the same costs and events as a patient receiving standard therapy, and that costs and events were uniformly distributed across each month. Residual benefits associated with gliflozin treatment following discontinuation were not captured in this analysis; therefore, we consider the assumption that discontinued patients incurred the same events as those who received standard therapy only to be conservative.

Annual costs for patients with ESKD were sourced from HAS [6, 7]. Medical transport costs were applied (€115.58 per round trip) to annual estimates of dialysis (assuming three round trips per week, €18,030.48) and transplant follow-up costs (assuming twelve trips per year, €1386.96).

Management of all treatment-related adverse events were assumed to require hospitalisation. The number of stays specific to each event were associated with the corresponding diagnosis-related group (DRG) cost, selected by ICD-10 code associated to each event. Palliative care was assumed to be provided in a hospital setting, with stays selected based on representative DRGs [34].

In line with current guidance for budget impact analyses, no discount was incorporated in the analysis [28, 29]. All costs are expressed in 2022 Euros (€); the consumer price index for health goods and services was used to adjust estimates for inflation [35]. Cost estimates applied in the model are shown in Table 2.

Scenario Analyses

In addition to the central scenario, lower and upper scenarios are considered to assess the influence of increasing the rates of diagnosis and enrolment in cardio-renal protective gliflozin therapy. The “lower scenario” assumes no such intervention is taken and in line with expected market developments as per standard practices. The “upper scenario” considers that stronger public health interventions are enacted, further increasing rates of patient diagnosis (approximately doubling the eligible population by year 5) and greater, but not uniform, enrolment on gliflozin therapy after diagnosis than modelled in the ‘central scenario’.

Table 2 Cost inputs

Inputs	Value (€) ^a
Annual costs	
Acquisition (gliflozins) ^b	484 [33]
Acquisition (standard therapy) ^b	57 [37]
Management (gliflozins)	522 [38–41]
Management (standard therapy)	493 [38–41]
Transplant monitoring	15,237 [6, 7]
Dialysis	79,577 [6]
Event costs	
Hospitalisation for heart failure	3024 [34]
Abrupt decline in kidney function	3260 [34]
Kidney transplant	68,828 [6, 42]
End-of-life care	5655 [34]
Volume depletion	2815 [34]
Major hypoglycaemia	1365 [34]
Fracture	1737 [34]
Diabetic ketoacidosis	2587 [34]
Amputation	7948 [34]

^aAll costs were varied by 20% in the deterministic sensitivity analysis

^bDrug acquisition costs incorporate product dispensing fees

Each of these three scenario analyses were further extended over 10-years to estimate the interval of the expected budget impact of introducing gliflozins, according to market share projections over a 10-year period. Population forecast estimates are disseminated in the supplementary materials (Supplementary Material Table S1).

Deterministic Sensitivity Analysis

One-way deterministic sensitivity analyses were conducted by varying event rates and cost inputs by $\pm 20\%$ to assess the model sensitivity to these parameters, and to evaluate uncertainty in the model simulation for the 5-year “central scenario” (base case).

Statement of Ethics Compliance

This study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. This study did not require informed consent or institutional/ethical review board approval, because it was based on previously conducted clinical trials, and does not contain any new studies with human participants or animals performed by any of the authors. Any data used to the purpose of the present study were anonymised.

RESULTS

Central Analysis

In the central scenario of improved public health intervention in CKD in a world with gliflozins, the eligible population was predicted to increase by 262,746 in year 5 (year 1: 379,000; year 5: 641,746). Market penetration of gliflozins was predicted to lead to 275,951 patients being treated with gliflozins in addition to standard therapy in year 5 alone, with 365,795 patients were treated with standard therapy only in year 5 alone (Table 3). Over the course of the 5-year period, patients were predicted to spend 598,650 patient-years being

Table 3 Clinical outcomes for the central scenario over a 5-year time horizon

	Year 1	Year 2	Year 3	Year 4	Year 5	Cumulative
Patients treated (patient-years)						
World without gliflozins						
Standard therapy	379,000	416,689	479,318	553,917	641,746	2,470,670
World with gliflozins						
Gliflozin + standard therapy	2143	26,772	105,859	187,925	275,951	598,650
Standard therapy	376,857	389,917	373,459	365,992	365,795	1,872,020
Clinical outcomes (total events)						
World without gliflozins						
≥ 50% sustained decline in eGFR	17,750	19,516	22,449	25,943	30,056	115,714
End-stage kidney disease	14,122	15,527	17,860	20,640	23,913	92,062
Dialysis	8728	9595	11,038	12,756	14,778	56,894
Transplant	5395	5931	6823	7885	9135	35,168
Hospitalisation for heart failure	6012	6609	7603	8786	10,179	39,190
Abrupt decline in kidney function	7500	8245	9485	10,961	12,699	48,889
All-cause mortality	4798	5275	6068	7013	8125	31,279
World with gliflozins						
≥ 50% sustained decline in eGFR	17,705	18,948	20,206	21,961	24,209	103,030
End-stage kidney disease	14,095	15,190	16,528	18,274	20,439	84,526
Dialysis	8711	9387	10,214	11,294	12,631	52,237
Transplant	5384	5802	6314	6981	7808	32,289
Hospitalisation for heart failure	5995	6398	6767	7302	8000	34,461
Abrupt decline in kidney function	7487	8088	8861	9853	11,072	45,360
All-cause mortality	4787	5139	5528	6053	6715	28,221
Incremental						
≥ 50% sustained decline in eGFR	- 45	- 567	- 2243	- 3982	- 5847	- 12,684
End-stage kidney disease	- 27	- 337	- 1333	- 2366	- 3474	- 7536
Dialysis	- 17	- 208	- 824	- 1462	- 2147	- 4657
Transplant	- 10	- 129	- 509	- 904	- 1327	- 2879
Hospitalisation for heart failure	- 17	- 211	- 836	- 1484	- 2180	- 4729
Abrupt decline in kidney function	- 13	- 158	- 624	- 1108	- 1627	- 3529

Table 3 continued

	Year 1	Year 2	Year 3	Year 4	Year 5	Cumulative
All-cause mortality	– 11	– 137	– 541	– 960	– 1410	– 3058

Event numbers are rounded, and so values for the cumulative event rates may differ. Negative values indicate the reduction in events incurred in the “world with gliflozins” scenario versus the “world without gliflozins” scenario
eGFR estimated glomerular filtration rate

treated with gliflozins versus 1,872,020 patient-years treated with standard therapy alone.

In the central scenario, gliflozin therapy was predicted to reduce the rate of disease progression compared to standard therapy. Cumulatively, the introduction of gliflozins led to 12,684 fewer patients with a $\geq 50\%$ sustained decline in *eGFR* (103,030 vs. 115,714) and 7536 fewer patients progressing to ESKD (84,526 vs. 92,062) over the 5-year time horizon, including 4657 fewer incidents of dialysis initiation, translating as up to 8458 fewer life-years spent on dialysis over the modelled horizon.

Gliflozin therapy was also predicted to lead to fewer adverse cardio-renal events, including 4729 fewer incidents of hospitalisation for heart failure (with gliflozins: 34,461; without gliflozins: 39,190), and 3529 fewer incidents of abrupt decline in kidney function (with gliflozins: 45,360; without gliflozins: 48,889). The introduction of gliflozins was projected to reduce the rate of death from any cause, with 3,058 fewer people dying over the 5-year horizon (with gliflozins: 28,221; without gliflozins: 31,279), translating as up to an estimated 5553 life years saved over the modelled horizon.

Total projected annual costs and 5-year cumulative cost estimates are detailed in Table 4, and are also illustrated in Supplementary Material Fig. S1. In year 5 alone, gliflozin therapy led to expected savings of – €361 million in France, with a cumulative 5-year saving of – €650 million. In the scenario without gliflozins, treatment of CKD with standard therapy was associated with a cumulative 5-year budget impact of €17.1 billion, of which €15.2 billion (89%) are due to the management of ESKD, with €1.36 billion (8%) resulting from drug acquisition and management costs. In the scenario with gliflozins, CKD management was

associated with a cumulative 5-year budget impact of €16.5 billion, with €14.3 billion (87%) due to ESKD management and a higher proportion of costs (€1.63 billion, 10%) from drug acquisition and management costs, respectively.

The introduction of gliflozins was estimated to avoid 4657 patients initiating dialysis and 2879 patients undergoing kidney transplants, leading to a total cost savings of – €78.4 million in year 3, rising to – €361 million at year 5, with – €650 million saved over the 5-year time horizon. Increased costs for drug acquisition and monitoring resulting from additive gliflozin therapy (€273 million) and management of adverse events (€2.98 million) were offset primarily by reduced costs relating to kidney events (ESKD, – €883 million; abrupt declines in kidney function, – €11.5 million) over the 5-year horizon. Treatment costs were further offset by costs relating to hospitalisation for heart failure (– €14.3 million) and end-of-life care (– €17.3 million). Overall, total costs were lower per patient treated with gliflozin than standard therapy only as a result of these offsets, and rose over time, costing – €1086 per year in those treated with a gliflozin in year 5 versus – €561 in year 1 (Table 4).

Scenario Analyses

The cumulative projected budget impact of gliflozin therapies in lower, central, and upper scenarios of early CKD diagnosis in the national adult population of France are provided in Table 5. In the lower scenario, introduction of gliflozins was estimated to yield budget savings of approximately – €340 million over a 5-year time horizon versus – €650 million in the central scenario. Budget savings were estimated to

Table 4 Budget impact outcomes for the central scenario over a 5-year time horizon

Annual cost breakdown (€)	Year 1	Year 2	Year 3	Year 4	Year 5	Cumulative
World without gliflozins						
Drug acquisition + management	208,362,527	229,082,717	263,514,266	304,526,418	352,812,194	1,358,298,122
Adverse events	19,660,698	21,615,817	24,864,713	28,734,543	33,290,699	128,166,470
End-stage kidney disease	1,065,817,853	1,922,844,221	2,899,869,734	4,008,193,352	5,271,852,637	15,168,577,798
Abrupt decline in kidney function	24,446,900	26,877,972	30,917,781	35,729,682	41,394,989	159,367,324
Hospitalisation for heart failure	18,177,598	19,985,232	22,989,049	26,566,959	30,779,422	118,498,259
All-cause mortality	27,132,442	29,830,572	34,314,162	39,654,661	45,942,312	176,874,149
Total	1,363,598,018	2,250,236,531	3,276,469,705	4,443,405,615	5,776,072,252	17,109,782,121
World with gliflozins						
Drug acquisition + management	209,338,869	241,279,924	311,743,181	390,144,234	478,534,214	1,631,040,421
Adverse events	19,671,350	21,748,882	25,390,868	29,668,593	34,662,266	131,141,960
End-stage kidney disease	1,063,781,854	1,896,001,845	2,780,383,877	3,742,218,839	4,803,427,957	14,285,814,371
Abrupt decline in kidney function	24,405,720	26,363,524	28,883,602	32,118,531	36,092,339	147,863,716
Hospitalisation for heart failure	18,126,412	19,345,779	20,460,592	22,078,345	24,188,298	104,199,425
All-cause mortality	27,070,544	29,057,301	31,256,572	34,226,709	37,971,857	159,582,982
Total	1,362,394,748	2,233,797,255	3,198,118,691	4,250,455,251	5,414,876,931	16,459,642,876
Incremental						
Drug acquisition + management	976,342	12,197,207	48,228,915	85,617,816	125,722,020	272,742,299
Adverse events	10,651	133,066	526,155	934,050	1,371,568	2,975,489
End-stage kidney disease	- 2,036,000	- 26,842,376	- 119,485,858	- 265,974,513	- 468,424,680	- 882,763,427
Abrupt decline in kidney function	- 41,180	- 514,449	- 2,034,178	- 3,611,152	- 5,302,649	- 11,503,608
Hospitalisation for heart failure	- 51,186	- 639,453	- 2,528,457	- 4,488,614	- 6,591,124	- 14,298,833
All-cause mortality	- 61,898	- 773,272	- 3,057,590	- 5,427,951	- 7,970,456	- 17,291,167
Total budget impact	- 1,203,270	- 16,439,276	- 78,351,014	- 192,950,364	- 361,195,322	- 650,139,246
Cumulative budget impact	- 1,203,270	- 17,642,546	- 95,993,560	- 288,943,924	- 650,139,246	N/A
Average cumulative savings per patient treated by gliflozins	- 561.49	- 610.15	- 712.25	- 895.40	- 1086.01	N/A

Negative values indicate the budget savings in the "world with gliflozins" scenario versus the "world without gliflozins" scenario

increase up to –€1.53 billion in the upper scenario.

Cumulative budget savings would also be expected to improve substantially in the longer term, with budget savings of approximately –€2.56 billion expected in the lower scenario of public health intervention (Table 5). In the central scenario, the cumulative cost savings were expected to rise to –€5.88 billion. In the upper scenario of improved implementation of public health interventions, savings would be expected to increase further to –€12.1 billion cumulatively, driven primarily by a reduction in patients progressing to ESKD (lower: 14,055, central: 33,468; upper: 67,644; Supplementary Material Table S2).

When considering the budget impact of gliflozins at a per patient-level, all scenarios demonstrated that treatment with gliflozins could be cost-saving versus those treated with standard therapy only (Table 5). Further, as coverage and duration of treatment increased over time in the longer term scenarios, the savings per patient would also increase. For example, in the central scenario the budget

savings per patient treated with gliflozins would increase (5-years: –€1,086; 10-years: –€2,211), driven by attenuated CKD progression and associated cardio-renal outcomes.

Deterministic Sensitivity Analysis

The tornado diagram presented in Fig. 3 shows that the estimated rates of progression to ESKD associated with both scenarios and ESKD cost inputs were highly influential on model outcomes. Nevertheless, the scenario with gliflozins led to budgetary savings in all analyses. Outcomes from deterministic sensitivity analyses on all considered parameters are presented in the supplementary materials (Supplementary Material Table S3).

DISCUSSION

The arrival of gliflozins as a potential therapeutic option for patients with CKD represents a significant departure from the past 20 years, where little innovation in direct drug therapy

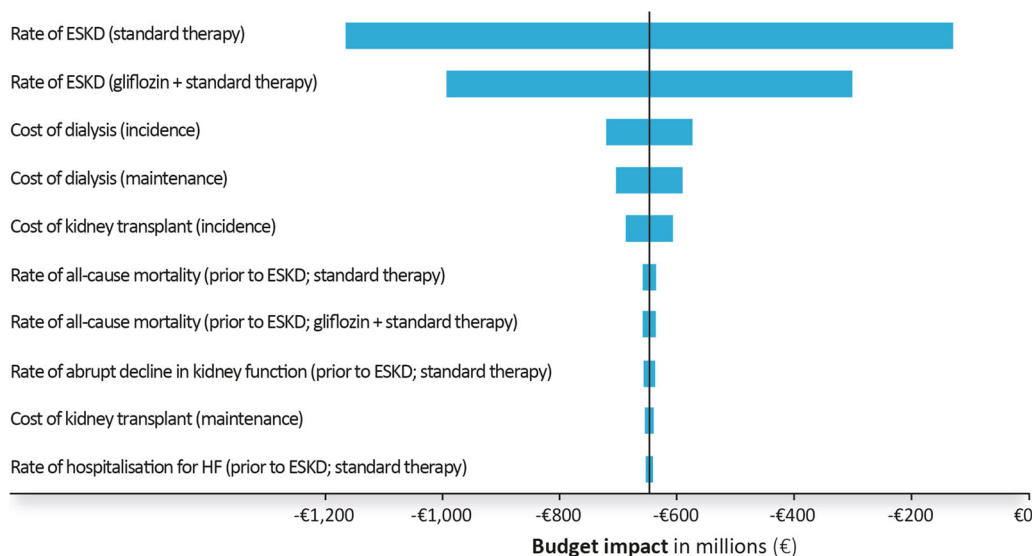


Fig. 3 Incremental budget impact model outcomes from deterministic sensitivity analyses. The vertical line indicates the total budget impact (–€650 million) over a 5-year horizon in the central scenario. All values (either costs or event rates) were varied to 80% and 120% of the base-case value. The ten parameter values that had the greatest

influence on the incremental budget impact model outcomes, in either direction, are presented here, with a full list of deterministic sensitivity analyses provided in Table S3 of the supplementary materials. *ESKD* end-stage kidney disease, *HF* heart failure

Table 5 Projected budget impact of gliflozins in different scenarios of public health action^a over a 10-year horizon

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Cumulative
Lower scenario of public health action											
Number treated (n)	379,000	380,445	381,860	383,249	384,615	385,963	387,296	388,617	389,928	391,229	3,852,202
World without gliflozins (thousands)	€1,363,598	€2,119,834	€2,854,005	€3,566,789	€4,258,849	€4,930,839	€5,583,397	€6,217,145	€6,832,685	€7,430,599	€45,157,738
World with gliflozins (thousands)	€1,363,172	€2,112,927	€2,809,589	€3,460,665	€4,076,764	€4,667,124	€5,236,269	€5,783,217	€6,301,689	€6,791,296	€42,602,714
Annual budget impact (thousands)	– €426	– €6906	– €44,415	– €106,124	– €182,085	– €263,714	– €347,128	– €433,929	– €530,996	– €639,302	– €2,555,024
Cumulative budget impact (thousands)	– €426	– €7332	– €51,747	– €157,871	– €339,957	– €603,671	– €950,799	– €1,384,727	– €1,915,722	– €2,555,024	N/A
Average cumulative savings per patient treated by gliflozin	– €561.49	– €602.38	– €671.28	– €893.28	– €1,133.91	– €1388.08	– €1644.42	– €1887.47	– €2098.25	– €2288.53	N/A
Central scenario of public health action											
Number treated (n)	379,000	416,689	479,318	553,917	641,746	705,921	737,687	763,506	776,486	781,921	6,236,190
World without gliflozins (thousands)	€1,363,598	€2,250,237	€3,276,470	€4,443,406	€5,776,072	€7,164,075	€8,524,404	€9,885,101	€11,208,864	€12,488,996	€66,381,221
World with gliflozins (thousands)	€1,362,395	€2,233,797	€3,198,119	€4,250,455	€5,414,877	€6,596,405	€7,726,737	€8,845,465	€9,921,233	€10,952,471	€60,501,954
Annual budget impact (thousands)	– €1,203	– €16,439	– €78,351	– €192,950	– €361,195	– €567,670	– €797,667	– €1,039,635	– €1,287,630	– €1,536,525	– €5,879,267
Cumulative budget impact (thousands)	– €1,203	– €17,643	– €95,994	– €288,944	– €650,139	– €1,217,810	– €2,015,476	– €3,055,111	– €4,342,742	– €5,879,267	N/A
Average cumulative savings per patient treated by gliflozin	– €561.49	– €610.15	– €712.25	– €895.40	– €1086.01	– €1297.05	– €1519.75	– €1749.66	– €1980.64	– €2211.40	N/A
Upper scenario of public health action											
Number treated (n)	379,000	462,450	543,621	640,536	754,748	813,781	870,556	929,265	992,217	1,059,746	7,445,920
World without gliflozins (thousands)	€1,363,598	€2,414,880	€3,598,506	€4,970,161	€6,562,287	€8,143,172	€9,787,684	€11,504,059	€13,302,293	€15,189,793	€76,836,432

Table 5 continued

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	Cumulative
World with gliflozins (thousands)	€1,360,957	€2,353,238	€3,386,758	€4,510,488	€5,764,328	€6,952,598	€8,166,421	€9,420,755	€10,728,860	€12,099,637	€64,744,040
Annual budget impact (thousands)	- €2641	- €61,642	- €211,748	- €459,673	- €797,959	- €1,190,574	- €1,621,263	- €2,083,304	- €2,573,433	- €3,090,156	- €12,092,392
Cumulative budget impact (thousands)	- €2641	- €64,283	- €276,031	- €735,704	- €1,533,663	- €2,724,236	- €4,345,499	- €6,428,803	- €9,002,236	- €12,092,392	N/A
Average cumulative savings per patient treated by gliflozin	- €536.03	- €588.62	- €768.53	- €961.69	- €1161.55	- €1382.16	- €1606.30	- €1827.55	- €2042.73	- €2250.30	N/A

Negative values indicate the budget savings in the "world with gliflozins" scenario versus the "world without gliflozins" scenario

*Public health action is defined as policy decisions and implementation of clinical guidelines, as outlined in the Methods, improving screening and awareness of at risk populations and more efficient access to medical care

has occurred since the introduction of RAASi therapies. It also presents a key opportunity to delay CKD progression and associated cardio-renal outcomes based on improving public health interventions. The presented budget impact analysis assesses the financial impact of increasing the numbers of screened, diagnosed and gliflozin-treated patients due to public health interventions in France, demonstrating budgetary savings in all considered scenarios.

The central scenario of public health intervention to improve rates of diagnosis and enrolment on effective treatments indicates that the introduction of gliflozins in France could lead to cost savings of -€650 million over 5 years. Overall costs per patient treated with gliflozins were lower than those treated with standard therapy. These savings were driven by attenuated CKD progression and avoidance of major cardio-renal events, with 4657 dialyses, 2879 transplants, 4729 hospitalisations for heart failure, and 3529 incidences of abrupt declines in kidney function avoided over the 5-year extrapolated period, as well as costs associated with 3058 fewer patients dying from any cause.

The alternative scenarios of public health intervention, providing upper and lower estimates of improved diagnosis rates and treatment coverage, indicate that increasing disease awareness and promoting earlier diagnoses may help reduce disease burden in France by up to €1.53 billion after 5 years. A further 10-year analysis considered potential savings to reach up to €12.1 billion in the upper scenario (with the most improved rates of screening and more patients being treated via public health policies), preventing up to an estimated 67,644 patients progressing to ESKD and 27,447 patients dying from any cause. Further, as market penetration increased in all scenarios, the overall cost savings per patient treated with gliflozins was also predicted to increase.

The implementation of public health policies aimed at optimising disease management, increasing disease awareness, and promotion of early diagnosis of CKD could reduce the rate of progression to ESKD and led to significant clinical and economic benefit to both patients and healthcare systems. The eligible population

is also expected to increase thanks to the Rémunération sur Objectifs de Santé Publique (Remuneration for Public Health Objective; an objective-based incentive for primary care physicians towards increased patient screening, diagnosing and access to treatment in hypertensive or diabetic patients) [36]. Other suggested public health interventions to achieve improved rates of diagnosis may include awareness campaigns targeting at-risk people to proactively discuss any concerns with their health-care professional. Further, the active participation of medical analysis laboratories, including the modification of reports and automated contacts with healthcare professionals, may increase identification of at-risk patients. Additionally, increased screening for early CKD via occupational physicians may improve rates of detection. It should be noted that these are only suggested policies and that implementation of alternative policies, focusing on improved diagnosis rates of patients in the earlier stages of CKD, may also achieve the same purpose.

The analysis described here is subject to limitations. This analysis is representative of patients eligible for the DAPA-CKD trial (eGFR, 25–75 ml/min per 1.73 m²; UACR, 200–5000 mg/g), and therefore this analysis is not able to predict the effects in patients with other characteristics and lower eGFR (as the latest KDIGO 2022 guidelines consider patients with an eGFR > 20 ml/min/1.73 m²).

The efficacy of empagliflozin according to the recently published results of the EMPA-KIDNEY trial have led to expectations that it will be an emerging treatment option in the future [19]. While the efficacy parameters of empagliflozin were not incorporated in this analysis, future analysis could be expanded to account for patients enrolled in EMPA-KIDNEY, who typically had patients with more advanced, higher-risk CKD and a higher rate of T2D. Further, consideration could also be given to patients treated with gliflozins for other purposes (e.g. T2D or heart failure) that present with CKD but do not fulfil DAPA-CKD inclusion criteria (i.e. UACR < 200 mg/g).

Finally, costs associated with increasing the size of the population screened, diagnosed and

enrolment on gliflozins were not included in the model, thus further analyses may be required to obtain a more precise estimation of the budget impact associated to gliflozins' introduction upon the implementation of necessary public health interventions. However, we anticipate that the costs associated with public health interventions would be limited, relative to the benefit that would be expected from early detection and treatment of CKD, and the offsets from reduced healthcare burden would exceed the expected cost of such public health interventions.

CONCLUSIONS

Our budget impact analysis predicts that treating patients with CKD with gliflozins in addition to standard therapy could offer great clinical, humanistic and economic benefit by slowing the rate of disease progression, leading to fewer adverse cardio-renal outcomes and lower total costs attributable to the French healthcare system. Concerted nationwide efforts can improve the rate of early CKD diagnosis via healthcare initiatives that increase the number of patients screened for evidence of CKD. Subsequent enrolment on protective therapies may have substantial benefit to the population of patients with CKD while preventing later healthcare resource use, leading to considerable budgetary savings.

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(ICMJE) criteria for authorship of this article, take responsibility for the integrity of the work, and have approved the article for publication.

Author Contributions. Juan Jose Garcia Sanchez and Roch Poulmais conceptualised and designed the study. Julie Chevalier, Meriem Boussahoua, and Peter Gabb were responsible for data analysis. Peter Gabb was responsible for preparation of the manuscript outline and subsequent drafts, collating and incorporating author comments and preparing tables and figures. Gérard de Pouvourville, Patrick Rossignol, Meriem Boussahoua, Julie Chevalier, Peter Gabb, Roch Poulmais, Dorian Verboux, Naveen Rao, Elisabeth Sörstadius, and Juan Jose Garcia Sanchez contributed to interpretation of the results, preparation and review of the manuscript, and approval of the final manuscript for publication.

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Compliance with Ethics Guidelines. This study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. This study did not require informed consent or institutional/ethical review board approval because it was based on previously conducted clinical trials and does not contain any new studies with human participants or animals performed by any of the authors. Any data used to the purpose of the present study were anonymised.

Data Availability. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>.

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