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Beyond Clinical Trials - The cost-saving associated with dapagliflozin use in portuguese hospital clinical practice

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Além dos ensaios clínicos - a redução de custos associada à utilização de dapagliflozina na prática clínica hospitalar em Portugal

Resumo

Introdução e Objetivos: A insuficiência cardíaca (IC) é uma síndrome clínica associada a uma elevada morbidade, mortalidade e despesa com custos de saúde. A dapagliflozina demonstrou ser eficaz na redução do risco de morte e hospitalização em doentes com IC, independentemente da fração de ejeção do ventrículo esquerdo. Este artigo visa projetar o potencial impacto da dapagliflozina na redução dos custos relacionados com hospitalizações subsequentes por IC em hospitais portugueses.

Métodos: Foi recolhido, e posteriormente analisado de forma agregada em *clusters*, o número total de hospitalizações por IC, hospitalizações subsequentes por IC e duração média de internamento dos doentes com diagnóstico primário de IC em seis hospitais portugueses, entre janeiro de 2019 e dezembro de 2021. Os custos relacionados com hospitalizações subsequentes por IC foram calculados de acordo com a legislação portuguesa e tendo em consideração três abordagens - conservadora, média e complexa. A projeção da redução de custos teve por base as reduções do risco relativo (RRR) de hospitalizações por IC (hIC) reportadas nos ensaios clínicos com dapagliflozina.

Resultados: Considerando uma RRR de 26% do risco de hospitalização subsequente por IC, com base no valor reportado na análise agregada dos estudos DAPA-HF e DELIVER relativa à RRR de hIC, a nossa projeção indica que a utilização da dapagliflozina resulta numa redução de custos. De acordo com a nossa projeção a redução de custos oscila entre €1,612,851.54 e €6,587,360.09, entre 2019 e 2021 ao considerar todos os hospitais envolvidos e as

diferentes abordagens metodológicas. A projeção aponta para um resultado similar tendo por base uma RRR de 24%, resultante da ponderação das subanálises de DAPA-HF e DELIVER, juntamente com dados epidemiológicos do estudo PORTHOS.

Conclusões: Nesta projeção, a utilização de dapagliflozina, em todos os doentes hospitalizados por IC que sejam elegíveis, está associada a uma redução direta significativa nos custos hospitalares. Estes dados reforçam a ideia de que, para além da melhoria nos resultados de saúde relacionados com a IC, a dapagliflozina pode ter um impacto significativo nos hospitais portugueses ao nível dos custos de saúde.

PALAVRAS-CHAVE

Insuficiência Cardíaca; iSGLT2; Dapagliflozina; Custos de saúde; Encargos económicos; Hospitalização por IC

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ABSTRACT

Introduction and Objectives: Heart failure (HF) is a clinical syndrome associated with substantial morbidity, mortality, and healthcare costs. Dapagliflozin has proven efficacy in reducing the risk of death and hospitalization in HF patients, regardless of left ventricular ejection fraction (LVEF). This paper aimed to project the potential impact of dapagliflozin on healthcare costs related to HF subsequent hospitalizations (HFHs) in Portuguese hospitals.

Methods: The total number of HF-related hospitalizations (hHF), HFHs, and the average length of stay for patients with a primary diagnosis of HF from six Portuguese hospitals, between January 2019 and December 2021, were collected and aggregated by hospital classification. Costs associated with HFHs were calculated according to Portuguese legislation and considering conservative, average, and complex approaches. Cost-saving projections were based on extrapolations from hHF risk reductions reported in dapagliflozin clinical trials.

Results: Considering a 26% risk reduction in hHF reported on pooled-analysis of DAPA-HF and DELIVER as the expected reduction in HFHs, the use of dapagliflozin would be associated with cost savings ranging from EUR 1 612 851.54 up to EUR 6 587 360.09, when considering all hospitals and the different approaches, between 2019 and 2021. A similar projection is observed based on 24% RRR derived by weighting DAPA-HF and DELIVER sub-analyses and PORTHOS epidemiological data.

Conclusions: In this projection, dapagliflozin use in all eligible hHF patients is associated with a significant reduction in direct costs. Our data support that, in addition to the improvements in HF-related outcomes, dapagliflozin may have a significant economic impact on healthcare costs in Portuguese hospitals.

KEYWORDS: Heart failure, SGLT2i, dapagliflozin, healthcare costs, economic burden, HF hospitalization.

INTRODUCTION

Heart failure (HF) stands as a pressing public health issue, exerting a substantial negative impact on healthcare costs and quality of life for those affected.¹⁻³ HF affects more than 64 million people worldwide, including 15 million in Europe.^{1,4,5} The Heart Failure Association Atlas 2019 report showed a median HF incidence in Europe of three per 1000 person-years for all ages and a median prevalence of 17 cases per 1 000 people, while data from EPICA study, published in 2002, reported a prevalence of 43.6 cases per 1000 people.^{2,6} It is expected that prevalence will increase with an aging population, in addition to the extended survival observed in patients following guideline-directed medical therapy (GDMT).⁷⁻⁹ Recently, in Portugal, data from the PORTHOS observational study were presented showing an HF prevalence of 16.54% in the population aged 50 years or more, according to an updated and guideline-based diagnosis approach (Rui Baptista and Cristina Gavina, personal communication, December 12, 2023).

Heart failure has a major economic impact and implies high direct and indirect costs.¹⁰ Hospital care, due to the high rate of hospitalizations, is the major driver of HF costs.¹⁰ Not only does HF represent a significant economic burden to the healthcare systems, accounting for 1% to 3% of global health expenses, but the costs associated with in-hospital treatment are estimated to represent 39% to 75% of the total HF costs.^{3,11} More than one million hospitalizations deriving from HF have been reported in Europe and America per year, as well as readmission rates of 30% and multiple readmissions.^{1,12} Following an HF diagnosis, patients are hospitalized, on average, once per year.¹³ Globally, the number of hospitalizations may be expected to increase by up to 50% in the next 25 years, due to the aging population and the increased prevalence of comorbidities.^{14,15} In Portugal, 39% of the costs associated with HF derive from hospitalizations.³ As HF prevalence in Portugal is expected to increase by 30% by 2035, the total costs are also predicted to rise to EUR 503 million during the next decade.³

Simultaneously, a rise in the in-hospital mortality can be expected.¹⁶ Effective treatments that allow a reduction in HF-related hospitalizations (hHF) can play a significant role in the reduction of long-term HF costs.³

Several successful HF therapies have been developed in recent years. Among them, SGLT2 inhibitors (SGLT2i), including dapagliflozin, and empagliflozin, have been shown to reduce the risk of cardiovascular death and hospitalization in HF patients.^{17,18} First, SGLT2i have proven their efficacy in patients with HF and reduced ejection fraction (HFrEF).^{19,20} In 2021, the results of the SOLOIST-WHF trial showed the benefits of sotagliflozin, a dual SGLT2 and SGLT1 inhibitor, in reducing deaths from cardiovascular causes, hospitalizations, and urgent visits for HF in patients with diabetes and recent worsening HF, regardless of EF.²¹ Then, the EMPEROR-Preserved trial and DELIVER showed the benefit of SGLT2i in HF patients with mildly reduced (HfmrEF) and preserved ejection fraction (HfpEF), regardless of type 2 diabetes.^{22,23} Additionally, the DELIVER study showed benefits for patients who were hospitalized or had been recently hospitalized with HF, and for those with HF with improved LVEF.^{23,24}

Both the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guidelines recommend SGLT2i use in the treatment of patients with HFrEF, regardless of diabetes status (class of recommendation I, level of evidence A) due to the beneficial role in decreasing hHF and mortality.^{25,26} SGLT2i are also recommended for the treatment of patients with both HfmrEF and HfpEF (class of recommendation I, level of evidence A and class of recommendation II, level of evidence B, according to the ESC and AHA/ACC/HFSA guidelines, respectively).^{25,27}

The benefit of SGLT2i across all HF patients, regardless of LVEF, represents a significant breakthrough, particularly for patients with HfpEF who had no previously effective therapeutic

options except for control of comorbidities and symptomatic relief.^{22,23} Given the high prevalence of HfpEF, the opportunity SGLT2i bring is considerable. Therefore, considering the economic burden of HF and the robust evidence that consolidates the unique role of SGLT2i, we aimed to gather insights on the impact dapagliflozin might have on cost outcomes had it been used in a hospital setting. For this purpose, we hypothesized that the use of in-hospital dapagliflozin to all eligible patients will be associated with a decrease in healthcare costs associated with HF subsequent hospitalizations (HFHs) in six Portuguese hospitals.

OBJECTIVES

Using a modeling approach that was informed by clinical study results, epidemiological data, and real-world evidence data, the aim of this paper was to project the economic impact of dapagliflozin on HFHs when started on patients who were hospitalized for HF.

METHODS

Population

For this economic projection, we gathered information from six Portuguese hospitals and included patients hospitalized with a primary HF diagnosis between the years of 2019 and 2021 retrospectively. The HF diagnosis was coded in accordance with the International Classification of Diseases (ICD) ninth and tenth revisions (Table S1 and S2). Considering the renal restrictions associated with dapagliflozin use (estimated glomerular filtration rate [eGFR] must be $>25\text{mL/kg/1.73m}^2$ for treatment initiation), we adjusted the population eligible for dapagliflozin in this projection by considering data from renal function characterizations documented in an available Portuguese HF cohort.²⁸ Specifically, to be conservative, we excluded 19% of coded HF patients due to a $\text{eGFR} < 30\text{mL/kg/1.73m}^2$, according to published

data.²⁸ For an additional projection, we excluded a further 44.7% of patients corresponding to HF patients with diabetes, as reported in the literature.²⁹ The data collected were then aggregated and analyzed based on hospital clusters: university hospitals (2), non-university hospitals (2) and HF clinics (2).³⁰ Additionally, we performed an independent analysis of dapagliflozin-associated cost reduction by using previously published HF Portuguese data.³¹

Assumptions for heart failure cost projection

The estimated cost per day of HFHs was determined by calculating the mean in-patient daily cost (overnight costs) and hospitalization prices (maximum costs of hospitalization, influenced by other factors, such as comorbidities) in accordance with Portuguese legislation (Table S3).³² The cost projection was conducted using three approaches (conservative, average and complex), taking into consideration the costs associated with the four levels of HF severity (minor, moderate, major, or extreme)³² (Table S3). In the conservative approach, the cost associated with the lower level of severity for all HF patients was used, resulting in a HFHs cost per day of EUR 876.07. The average approach was estimated by calculating the average of the cost values associated with the four levels of severity, amounting to EUR 1 859.98 per day. Finally, the complex approach used the cost value associated with the highest level of severity (extreme), totaling EUR 3 568.44 per day (Table S4).³²

Concerning medication costs, only dapagliflozin treatment was considered, excluding other interventions (drugs or devices). Based on the assumptions that other treatments were used equally independently of dapagliflozin, excluding costs of other treatment would not impact the cost reduction associated with dapagliflozin.

Clinical inputs regarding HFHs Cost-saving projection

For the projection of HFHs-related savings associated with dapagliflozin use in hHF patients, we utilized the collected aggregated data by clusters of hospitals and the dapagliflozin reported

outcomes in clinical trials as inputs to our projection model. We projected two scenarios on HFHs cost reduction by extrapolating expected risk reductions on HFHs based on the hHF relative risk reductions obtained in the DAPA-HF and DELIVER clinical trials.^{19,23} Scenario A considered a 26% expected reduction on HFHs. In the DAPA-HF & DELIVER pooled-analysis the reported relative risk associated with dapagliflozin for a first hHF and total HF hospitalizations were 26% and 29%, respectively. Therefore, to be cautious, we considered the value reported for the first hHF as an extrapolation for the projection of HFHs in our model, given that the reduction in HFHs-associated risk in the DAPA-HF and DELIVER pooled-analysis likely falls >29%. The scenario B considered an expected HFHs extrapolated from the 36% hHF relative risk reduction in HFfrEF patients with a previous hospitalization in less than one year, and a 24% risk reduction in both HfmrEF and HfpEF patients that were recently hospitalized^{33,34}. Since the data collected from the Portuguese hospitals did not differentiate among the HF phenotypes, we used the recent data from PORTHOS study to weight the values extrapolated from the literature according to PORTHOS HF phenotype reported prevalence. Thus, since PORTHOS reported a prevalence of 0.35%, 0.97% and 15.22% for HFfrEF, HfmrEF and HfpEF in mainland Portugal (Rui Baptista and Cristina Gavina, personal communication, December 12, 2023), we considered a reduction of 24% of hHF risk, according with the formula: % risk reduction = (0.36 x 0.02) + (0.24 x 0.98), where the 2% and 98% are the proportion of Portuguese HF patients with either HFfrEF or HfmrEF and HfpEF, respectively. For projections, we used the collected data and calculated the costs associated with patient subsequent hospitalizations using the values described above. The details of projections are illustrated in Table S5.

RESULTS

Hospitalization and patient characteristics

Between January 2019 until December 2021, a total of 4,813 hHF were registered in the enrolled hospitals. Among these, 81.5% corresponded to first-time hospitalizations, and 18.5% to HFHs. The average length of stay for readmissions was 10 days. Out of the total of hHF, 58.6% were registered at university hospitals, 38.0% in non-university hospitals, and only 3.4% in HF clinics. However, data from HF clinics were only collected for the year 2019 due to COVID-19 constraints.

Regarding patient's characteristics, 49.2% were female. The mean age of hHF patients was 78 years. Detailed information on the number of hospitalizations, average number of hospitalization days and patient's characteristics are expressed in Table 1.

Cost-saving associated with dapagliflozin use

The detailed costs associated with HFHs in the different hospital clusters, years, and approaches, as well as the savings associated with dapagliflozin using the two scenarios, are presented in Table 2. In scenario A we projected HFHs cost savings associated with dapagliflozin use, considering a 26% reduction in HFHs. At university hospitals, 2019 and 2021, dapagliflozin initiation was associated with a reduction of EUR 820 968.79, EUR 1 746 316.23, and EUR 3 353 078.00 in the conservative, average and complex approaches, respectively (Table 2). Similarly, projections applied to the non-university hospitals showed reductions in HFHs costs of EUR 758 896.63, for the conservative approach; EUR 1 614 280.02 in the average approach; and EUR 3 099 557.07 for the complex approach, in the same years (Table 2). In 2019, the implementation of dapagliflozin in HF clinics was associated with reductions of EUR 32 986.12, EUR 70 166.12, and EUR 134 725.02 considering the conservative, average and complex approaches, respectively (Table 2). According to our model, cost savings associated with the implementation of dapagliflozin for all eligible hHF

patients could range from EUR 1 612 852 in the conservative approach, to EUR 6 587 360 in the complex approach.

In scenario B, in the conservative approach, we observed cost reductions of EUR 765 125.30 for the university hospitals between 2019 to 2021. In the average approach, the cost savings were EUR 1 627 833.84 for the same years. In the complex approach, we observed a cost reduction of EUR 3 125 830.19 (Table 2). Applying this second projection to data from non-university hospitals, we observed a reduction in HFHs costs of EUR 707 275.38, EUR 1 504 755.90, and 2 889 491.11 in the same years, considering the conservative, average and complex approaches, respectively (Table 2). Finally, in HF clinics, the cost savings associated with dapagliflozin considering a 24% reduction of HFHs risk were EUR 30 742.36 in the conservative approach, EUR 65 405.56 in the average approach, and EUR 125 594.31 in the complex approach (Table 2). Overall, in scenario B the use of dapagliflozin, and taking into account all years in the study this projection indicates a cost reduction up to EUR 6 140 916. SGLT2i were already widely used in HF diabetic patients, therefore, a significant proportion of patients in our analysis could have previously taken or started an SGLT2i, which has a proven impact on HFHs. To address this limitation, we performed an independent analysis excluding 44.7% of patients corresponding to the reported diabetes incidence among HF patients.²⁹ Even excluding these patients, cost savings associated with dapagliflozin implementation can reach EUR 718 501.50, EUR 1 528 353.89, and EUR 2 934 571.47 in the conservative, average and complex approaches, respectively, when considering the 26% HFHs risk reduction for all the years and hospitals in the study (Table S6). Taking into account the 24% HFHs risk reduction, cost savings range between EUR 669 627.99, EUR 1 424 659.60 and EUR 2 735 687.07 in the conservative, average, and complex approaches for all hospitals and years analyzed (Table S6).

Cost-saving associated with dapagliflozin use in previous published Portuguese heart failure cohorts

According to the literature, between 2012 and 2014, 51 310 patients with a primary diagnosis of HF were hospitalized in Portuguese hospitals.³¹ From these, 22.1% were considered heavy users, meaning that they had two or more HF admissions within a 365-day period.³¹ According to the same study, the length of hospital stay for frequent users was at least 20 days.³¹ Taking into consideration these data, according to scenario A, dapagliflozin could have saved EUR 41 486 961.55, EUR 88 248 610 or EUR 169 444 954 considering the conservative, average, and complex approaches, respectively between 2012 and 2014. If we consider scenario B cost savings reach the EUR 38 664 958.16, EUR 82 261 202.84, and EUR 157 961 178.47 in each approach.

DISCUSSION

Heart failure is related to significant morbidity and mortality, representing an important social and economic burden.³⁵ The increasing aging of the population, and the improvement in healthcare including innovative secondary prevention therapy and rehabilitation programs, are factors that highly contribute to the rising incidence and prevalence of this condition.³ According to the literature, HF costs represent 2.6% of total Portuguese public health expenditure.³ Furthermore, costs related to HF admissions represent 1.6% of Portuguese hospitals' budgets, and over 41% of these costs are attributed to patients that are re-hospitalized at least once within one year after previous discharge.³¹ Given this approach, the approval of therapies that significantly reduce hHF risk can have an important impact on healthcare costs. Dapagliflozin was associated with a reduction in the number of HF hospitalizations and subsequent hospitalizations.^{33,34,36} In this paper, we projected the impact of in-hospital

dapagliflozin use on healthcare costs related to HF readmissions by analyzing aggregated data collected from different Portuguese hospitals. The complexity of HF management in an hHF setting varies significantly, influenced by factors such as whether it is the first or a repeated event, comorbidities, the severity of the condition, the type of hospitalization and medical specialty. Therefore, for simplification, in this projection, the data were aggregated into three different approaches. Although the data used for the projection may not be representative of the national reality, this approach aimed to create a simple and comprehensive approach that reflects the economic impact of dapagliflozin use in all eligible patients in the different healthcare infrastructures (in terms of size) where an HF patient can be managed. Categorization of the data collected by the hospital sources provides a snapshot of these savings in these three different realities. We also evaluated data from HF clinics. Although these clinics can be placed in university and non-university hospitals, we also aimed to evaluate the impact of dapagliflozin in this setting since it is an increasing practice for patient management in our country. Our findings demonstrate that the use of in-hospital dapagliflozin for all eligible HF patients is associated with a significant decrease in costs in all considered approaches. Our projection model is based on the reported reduction of hHF risk associated with dapagliflozin use. Specifically, we project the HFHs cost savings associated with dapagliflozin use based on extrapolations for expected HFHs relative reductions based on data available from DAPA-HF and DELIVER clinical trials.^{33,34} Both DAPA-HF and DELIVER studies were multinational, double-blinded, placebo-controlled randomized clinical trials in patients with HFrEF and with mildly reduced, preserved, or improved LVEF, respectively. These studies evaluated the efficacy and safety of 10 mg dapagliflozin, daily, in comparison with placebo over a follow-up of 18.2 months (DAPA-HF) and 2.3 years (DELIVER).^{19,23}

In scenario A, dapagliflozin was associated with HFHs cost savings ranging from EUR 32 986.12, when applied to HF clinics in 2019, considering a conservative approach, to EUR 1

390 808.69, when considering the complex approach with data collected from 2019 in university hospitals. Similarly, if we consider the scenario B, cost savings can reach EUR 1 296 549.56 in the case of university hospitals in 2019. For these projections, we specifically focused on the medication expenses attributed to dapagliflozin only. This decision stemmed from our assumption that the utilization of other HF medications would likely maintain a similar rate, irrespective of dapagliflozin use. Moreover, our analysis presumed that the benefits associated with dapagliflozin remain constant regardless of variations in other patterns of HF treatment, as previously reported in the literature.^{37,38}

In the university hospitals cluster, the use of dapagliflozin in the represented years could involve savings of EUR 813 916.92 per hospital in an average approach. Considering that Portugal has seven university hospitals, savings could reach EUR 5 697 418.43 in these years.³⁹ Additionally, for non-university hospitals extrapolation we only considered hospitals equipped a cardiology unit. We estimate an average cost reduction of EUR 752 377.95 per hospital resulting in a potential total cost reduction of EUR 22 571 338.43 for all the 30 Portuguese non-university hospitals with a structured cardiology unit.³⁹ Notwithstanding, it is relevant to highlight that many HF patients are managed by internal medicine, and the role of internal medicine is paramount in the management of patients with acute HF. For simplification purposes, we assumed only these 30 hospitals, however even hospitals without a structured cardiology unit might benefit of cost savings associated with dapagliflozin use. Moreover, non-university hospitals vary in size, resources, and population served, and thus this value may be biased; the projection indicates the economic impact that dapagliflozin can have among Portuguese hospitals..

Regarding the HF clinics, although they have grown significantly internationally and even nationally in recent years, there is no information available on the exact number of HF clinics in our country. Therefore, we are unable to estimate the total savings that the use of

dapagliflozin can generate in this context. Nevertheless, from the independent projection, our model pointed to potential significant savings. Overall, according to scenario B, Portuguese healthcare costs could be reduced in EUR 28 268 756.86 through the treatment with dapagliflozin to all eligible patients. It is also important to notice that even after excluding a significant percentage of patients corresponding to the HF diabetic population already treated with SGLT2i, our projections still indicate a significant cost-saving associated with dapagliflozin use.

Despite not intended to be a cost-effectiveness study, the results from our projections are aligned with previous cost-effectiveness studies, in which the use of dapagliflozin was a cost-effective treatment for HF_rEF relative to GDMT when evaluated in various healthcare systems, including the US⁴⁰, UK, German, and Spain.⁴¹ A similar conclusion is indicated by recent cost-effectiveness studies of dapagliflozin in HfmrEF and HfpEF patients.^{42,43}

In this projection, we considered data from HF readmissions coded as the main diagnosis, opting for conservative yet more accurate projection. Nevertheless, the cost savings could potentially be higher in clinical practice, when considering all hHF, given that hHF is often recorded as a secondary cause of readmission. Additionally, we focused only on the direct cost of patients' readmissions to estimate cost savings. However, HF also represents a burden on patients' quality of life, impacting the daily living activities of patients and their caregivers.¹⁰ Given the impact of dapagliflozin in improving HF-related outcomes, its implementation can also contribute to improvements in-patients' quality of life.

We also applied our methodology to calculate the savings associated with hHF according to the Portuguese published data. Between 2012 and 2014, 51 310 patients with a main diagnosis of HF have been hospitalized in Portuguese hospitals³¹, leading to 68 565 admissions and 665 000 bed-days. The inpatient hospital services cost associated with these hospitalizations amounted to EUR 193 million, which corresponds to nearly 1.6% of the total costs from the

national healthcare service.³¹ From the 51,310 admitted patients, 22.1% had an average of 2.5 inpatient admissions per year, while 21.8% of these patients were re-hospitalized within 30 days, and 54.9% within 90 days of discharge.³¹ Considering this data and an average approach, the national health service could have saved up to EUR 82 261 202.84 if dapagliflozin had been available and implemented at that time.

On average, 19% of our sample HF patients were re-hospitalized at least once after a previous HF hospitalization. This aligns with published national results showing a subsequent hospitalizations rate of 22.10%.³¹ Our data is also consistent with the literature regarding the average age of patients (78 years for both) and gender distribution (51% female patients in our sample compared with 56% in published data).³¹ According to our data, the average length of stay for acute HF subsequent hospitalizations was approximately 10 days, which is lower than reported in previous studies.³¹

Limitations

This projection has several limitations that should be acknowledged. The clusters have only two sources which is not sufficient for a comprehensive representation of the entire cluster. Moreover, a broad standard deviation demonstrates the variability between the two sources. The data collected spanned three years, including the period of the coronavirus pandemic (COVID-19), which significantly affected access to healthcare and patient willingness to seek medical help. In Portugal, the first patient with COVID-19 was diagnosed in March 2020, so the 2019 data was not influenced by the pandemic. If HF hospitalization rates in 2020 and 2021 were similar to 2019, would increase the cost savings up to EUR 19 762 080.26 and EUR 18 422 746.86 considering 26% and 24% RRR on HFHs, respectively, in a complex scenario and for all considered hospitals. At the same time, we cannot rule out the worsening of HF conditions related with COVID-19. Therefore, our projection would benefit from the inclusion

of data collected in recent years either before or after the pandemic. Additionally, data regarding the use of out-patient services were not assessed, and for simplicity, other not expected costs have a significant impact on the projections performed were also not included. Similarly, costs related with dapagliflozin side effects were not considered.

Another limitation concerns the public nature of the hospitals from which our data were collected, as the costs associated with patients' follow-up in the private sector cannot be included, which could impact the reduction of health expenditure in the projections.. Moreover, and as shown by previous studies focusing on the QoL of HF patients^{36,45}, dapagliflozin may help further reducing indirect costs associated to absenteeism related to consultations, emergency visits and hospitalizations. However, the evaluation of these costs falls outside the scope of this projection.

For this projection, we considered the recently presented data regarding HfrEF, HfmrEF and HfpEF incidence in Portugal (Rui Baptista and Cristina Gavina, personal communication, 12 December 2023). However, the characteristics of the inpatient population may not reflect this incidence since a higher number of hospitalizations due to HF_rEF is expected when compared with the other forms of HF. For projection purposes, we assumed that all eligible HF patients initiated dapagliflozin treatment during their first hHF event each year (index hHF). However, it is plausible that some of these eligible patients might have been already receiving dapagliflozin treatment. To strengthen our conclusions, we performed a separate analysis excluding the percentage of reported HF diabetic patients. Furthermore, it is worth noting that dapagliflozin had received approval in Europe for HF_rEF treatment, in addition to type 2 diabetes, by the end of 2020, and for HF treatment irrespective of LVEF in 2022. Considering the update of ESC HF guidelines occurred only in 2021, it is anticipated that the adoption rate of dapagliflozin treatment among non-diabetic HF patients from 2019 to 2021 remained relatively low.

Aside from the assumption mentioned above, our model has other important assumptions to be taken in consideration in the discussion of the results. Firstly, we considered only HF readmissions occurring within the same year to calculate the subsequent hospitalizations rate; secondly, the mean length of hospital stays was used instead of the median (which would be less impacted by possible outliers); thirdly, the calculated costs used were based on the Portuguese legislation and not in data specifically gathered from each hospital. Additionally, our data sources comprised only two hospitals for each group, contributing to increased standard deviation. However, despite these limitations, the results consistently indicate substantial cost reductions across all approaches tested within hospital settings.

CONCLUSIONS

Heart failure has a significant economic impact on healthcare costs, and this economic impact is expected to increase in the next years. A considerable proportion of HF costs are attributed to hospitalizations, which are frequently recurrent. We had no intention of developing a comprehensive cost-effectiveness model, but this simplified projection based on real-world data acts as a significant addition to the translation of clinical trial data into clinical practice. This paper underscores the vital importance of implementing scientific knowledge to everyday medical practice. Our projections point to a significant cost reduction in all tested approaches, highlighting the importance of dapagliflozin use in an economic context. In addition to the reported value of dapagliflozin in improving HF outcomes, our projection clearly indicates a substantial cost reduction associated with subsequent HF hospitalizations when dapagliflozin is started during a HF hospitalization in all HF eligible patients.

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Sí

REFERENCES

- 1 Seferovic, P. M.Jankowska, E.Coats, A. J. S. *et al.* The Heart Failure Association Atlas: rationale, objectives, and methods. *Eur J Heart Fail* **22**, 638-45 (2020). <https://doi.org/10.1002/ejhf.1768>
- 2 Seferovic, P. M.Vardas, P.Jankowska, E. A. *et al.* The Heart Failure Association Atlas: Heart Failure Epidemiology and Management Statistics 2019. *Eur J Heart Fail* **23**, 906-14 (2021). <https://doi.org/10.1002/ejhf.2143>
- 3 Gouveia, M. R. A.Ascensão, R.Fiorentino, F. *et al.* Current costs of heart failure in Portugal and expected increases due to population aging. *Rev Port Cardiol* **39(1)**, 3-11 (2020). <https://doi.org/10.1016/j.repc.2019.09.006>
- 4 Lawson, C. A.Zaccardi, F.Squire, I. *et al.* 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study. *Lancet Public Health* **4**, e406-e20 (2019). [https://doi.org/10.1016/S2468-2667\(19\)30108-2](https://doi.org/10.1016/S2468-2667(19)30108-2)

- 5 Groenewegen, A.Rutten, F. H.Mosterd, A. *et al.* W. Epidemiology of heart failure. *European Journal of Heart Failure* **22**, 1342-56 (2020). <https://doi.org/10.1002/ejhf.1858>
- 6 Ceia, F.Fonseca, C.Mota, T. *et al.* Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail* **4**, 531-9 (2002). [https://doi.org/10.1016/s1388-9842\(02\)00034-x](https://doi.org/10.1016/s1388-9842(02)00034-x)
- 7 Mosterd, A. Hoes, A. W. Clinical epidemiology of heart failure. *Heart* **93**, 1137-46 (2007). <https://doi.org/10.1136/hrt.2003.025270>
- 8 Zarrinkoub, R.Wettermark, B.Wandell, P. *et al.* The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. *Eur J Heart Fail* **15**, 995-1002 (2013). <https://doi.org/10.1093/eurjhf/hft064>
- 9 Komajda, M.Cowie, M. R.Tavazzi, L. *et al.* Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* **19(11)**, 1414-23 (2017). <https://doi.org/10.1002/ejhf.887>
- 10 Hessel, F. P. Overview of the socio-economic consequences of heart failure. *Cardiovascular Diagnosis and Therapy* **11**, 254-62 (2021). <https://doi.org/10.21037/cdt-20-291>
- 11 Dunlay, S. M.Shah, N. D.Shi, Q. *et al.* Lifetime costs of medical care after heart failure diagnosis. *Circ Cardiovasc Qual Outcomes* **4**, 68-75 (2011). <https://doi.org/10.1161/CIRCOUTCOMES.110.957225>
- 12 Lala, A.McNulty, S. E.Mentz, R. J. *et al.* Relief and Recurrence of Congestion During and After Hospitalization for Acute Heart Failure: Insights From Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF). *Circ*

- Heart Fail* **8**, 741-8 (2015).
<https://doi.org/10.1161/CIRCHEARTFAILURE.114.001957>
- 13 Barasa, A.Schaufelberger, M.Lappas, G. *et al.* Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden. *Eur Heart J* **35**, 25-32 (2014). <https://doi.org/10.1093/eurheartj/eh278>
- 14 Al-Mohammad, A.Mant, J.Laramee, P. *et al.* Diagnosis and management of adults with chronic heart failure: summary of updated NICE guidance. *BMJ* **341**, c4130 (2010). <https://doi.org/doi:10.1136/bmj.c4130>
- 15 Savarese, G. Lund, L. H. Global Public Health Burden of Heart Failure. *Card Fail Rev* **3**, 7-11 (2017). <https://doi.org/10.15420/cfr.2016:25:2>
- 16 Fonseca, C. Brás, D. Araújo, I. *et al.* Heart failure in numbers: Estimates for the 21st century in Portugal. *Rev Port Cardiol* **37(2)**, 97-104 (2018). <https://doi.org/10.1016/j.repc.2017.11.010>
- 17 Packer, M. SGLT2 inhibitors: role in protective reprogramming of cardiac nutrient transport and metabolism. *Nature Reviews Cardiology* **20**, 443-62 (2023). <https://doi.org/10.1038/s41569-022-00824-4>
- 18 Seferovic, P. M.Fragasso, G.Petrie, M. *et al.* Sodium-glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* **22**, 1495-503 (2020). <https://doi.org/10.1002/ejhf.1954>
- 19 McMurray, J. J. V.Solomon, S. D.Inzucchi, S. E. *et al.* Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* **381(21)**, 1995-2008 (2019). <https://doi.org/10.1056/NEJMoa1911303>

- 20 Wiviott, S. D. Raz, I. Bonaca, M. P. *et al.* Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* **380(4)**, 347-57 (2019). <https://doi.org/10.1056/NEJMoa1812389>
- 21 Bhatt, D. L. Szarek, M. Steg, P. G. *et al.* Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *New England Journal of Medicine* **384**, 117-28 (2021). <https://doi.org/10.1056/nejmoa2030183>
- 22 Anker, S. D. Butler, J. Filippatos, G. *et al.* Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med* **385(16)**, 1451-61 (2021).
- 23 Solomon, S. D. McMurray, J. J. V. Claggett, B. *et al.* Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *New England Journal of Medicine* **387**, 1089-98 (2022). <https://doi.org/10.1056/nejmoa2206286>
- 24 Vardeny, O. Fang, J. C. Desai, A. S. *et al.* Dapagliflozin in heart failure with improved ejection fraction: a prespecified analysis of the DELIVER trial. *Nat Med* **28**, 2504-11 (2022). <https://doi.org/10.1038/s41591-022-02102-9>
- 25 Heidenreich, P. A. Bozkurt, B. Aguilar, D. *et al.* 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. *Journal of the American College of Cardiology* **79**, e263-e421 (2022). <https://doi.org/10.1016/j.jacc.2021.12.012>
- 26 McDonagh, T. A. Metra, M. A. Adamo, M. *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* **24(1)**, 4-131 (2022). <https://doi.org/10.1002/ejhf.2333>

- 27 McDonagh, T. A. Metra, M. Adamo, M. *et al.* 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* **44**, 3627-39 (2023). <https://doi.org/10.1093/eurheartj/ehad195>
- 28 Maltês, S. Cunha, G. J. L. Rocha, B. M. L. *et al.* Dapagliflozin in a Real-World Chronic Heart Failure Population: How Many Are Actually Eligible? *Cardiology* **146**, 201-6 (2021). <https://doi.org/10.1159/000512432>
- 29 Gavina, C. Carvalho, D. S. Valente, F. *et al.* 20 Years of Real-World Data to Estimate the Prevalence of Heart Failure and Its Subtypes in an Unselected Population of Integrated Care Units. *Journal of Cardiovascular Development and Disease* **9**, 149 (2022). <https://doi.org/10.3390/jcdd9050149>
- 30 Fonseca, C. A Heart Failure Clinic. *European Heart Journal* **39**, 826-8 (2018). <https://doi.org/10.1093/eurheartj/ehy052>
- 31 Moita, B. A. -O. Marques, A. P. Camacho, A. M. *et al.* One-year rehospitalisations for congestive heart failure in Portuguese NHS hospitals: a multilevel approach on patterns of use and contributing factors. *BMJ Open* **9(9)**, e031346 (2019). <https://doi.org/10.1136/bmjopen-2019-031346>
- 32 Government, P. *Portaria n.º 207/2017, de 11 de julho*, <<https://diariodarepublica.pt/dr/detalhe/portaria/207-2017-107669157>> (2017).
- 33 Berg, D. D. Jhund, P. S. Docherty, K. F. *et al.* Time to Clinical Benefit of Dapagliflozin and Significance of Prior Heart Failure Hospitalization in Patients With Heart Failure With Reduced Ejection Fraction. *JAMA Cardiology* **6**, 499 (2021). <https://doi.org/10.1001/jamacardio.2020.7585>
- 34 Cunningham, J. W. Vaduganathan, M. Claggett, B. L. *et al.* Dapagliflozin in Patients Recently Hospitalized With Heart Failure and Mildly Reduced or Preserved Ejection

- Fraction. *J Am Coll Cardiol* **80**, 1302-10 (2022).
<https://doi.org/10.1016/j.jacc.2022.07.021>
- 35 Savarese, G. Becher, P. M. Lund, L. H. *et al.* Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovascular Research* **118**, 3272-87 (2023). <https://doi.org/10.1093/cvr/cvac013>
- 36 Jhund, P. S. Kondo, T. Butt, J. H. *et al.* Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nature Medicine* **28**, 1956-64 (2022). <https://doi.org/10.1038/s41591-022-01971-4>
- 37 Pabon, M. Claggett, B. L. Wang, X. *et al.* Influence of background medical therapy on efficacy and safety of dapagliflozin in patients with heart failure with improved ejection fraction in the DELIVER trial. *European Journal of Heart Failure* **25**, 1663-70 (2023). <https://doi.org/10.1002/ejhf.3001>
- 38 Docherty, K. F. Jhund, P. S. Inzucchi, S. E. *et al.* Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. *European Heart Journal* **41**, 2379-92 (2020). <https://doi.org/10.1093/eurheartj/ehaa183>
- 39 Direção-Geral da Saúde. *Rede de referência de Cardiologia*, <<https://www.sns.gov.pt/wp-content/uploads/2016/05/rede-referencia%C3%A7%C3%A3o-hospitalar-cardiologia-v.2015.pdf>> (2015).
- 40 Isaza, N. Calvachi, P. Raber, I. *et al.* Cost-effectiveness of Dapagliflozin for the Treatment of Heart Failure With Reduced Ejection Fraction. *JAMA Network Open* **4**, e2114501 (2021). <https://doi.org/10.1001/jamanetworkopen.2021.14501>
- 41 McEwan, P. Darlington, O. McMurray, J. J. V. *et al.* Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-

- economic analysis of DAPA-HF. *European Journal of Heart Failure* **22**, 2147-56 (2020). <https://doi.org/10.1002/ejhf.1978>
- 42 Booth, D.Davis, J. A.McEwan, P. *et al.* The cost-effectiveness of dapagliflozin in heart failure with preserved or mildly reduced ejection fraction: A health-economic analysis of the DELIVER trial. *European Journal of Heart Failure* **25**, 1386-95 (2023). <https://doi.org/10.1002/ejhf.2940>
- 43 Tang, Y. Sang, H. Cost-utility analysis of add-on dapagliflozin in heart failure with preserved or mildly reduced ejection fraction. *ESC Heart Failure* **10**, 2524-33 (2023). <https://doi.org/10.1002/ehf2.14426>
- 44 Meireles, M. A.Golçalves, J. Neves, J. Acute Heart Failure Comorbidome: The Impact of Everything Else. *Acta Med Port* **33(2)**, 109-15 (2020). <https://doi.org/10.20344/amp.11051>
- 45 Nassif, M. E.Windsor, S. L.Borlaug, B. A. *et al.* The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med* **27**, 1954-60 (2021). <https://doi.org/10.1038/s41591-021-01536-x>

TABLES

Table 1: Characteristics of heart failure admissions in study hospitals.

Variable	University Hospitals (N = 2)						Non-university Hospitals (N = 2)						HF Clinics (N = 2)	
	2019		2020		2021		2019		2020		2021		2019	
	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD	Mean (%)	SD
Total hospitalizations, mean	1,242	318.20	844	147.08	737	229.81	586	172.53	584	214.25	660	253.85	161	115.26
First-time hospitalizations, mean	1,053 (85%)	275.06	729 (86%)	121.62	627 (85%)	167.58	430 (73%)	71.42	449 (77%)	136.47	495 (75%)	154.86	139 (86%)	122.33
Subsequent hospitalizations, mean	189 (15%)	43.13	115 (14%)	25.46	110 (15%)	62.23	157 (27%)	101.12	135 (23%)	77.78	165 (25%)	98.99	22 (14%)	7.07
Length of stay in days, mean	10	0.42	11	0.76	12	2.03	9	1.14	8	0.17	10	1.51	8	0.31
Female patients, mean	521 (42%)		354 (42%)		310 (42%)		353 (60%)		356 (61%)		393 (60%)		79 (49%)	
Age in years, mean	75	4.07	75	4.08	75	3.63	81	0.15	81	0.36	82	0.56	77	0.28

HF, heart failure. SD, Standard deviation.

Table 2: Cost-saving projections for hospital readmissions associated with dapagliflozin use.

		Total cost of annual subsequent hospitalization	SCENARIO A (26% expected RRR on HFHs ^A)			SCENARIO B (24% RRR derived by weighting DAPA-HF, DELIVER with PORTHOS study ¹)		
			Conservative	Average	Complex	Conservative	Average	Complex
University Hospitals	2019	Without Dapagliflozin	€ 1,314,428.27	€ 2,790,662.33	€ 5,353,976.75	€ 1,314,428.27	€ 2,790,662.33	€ 5,353,976.75
		With Dapagliflozin	€ 973,902.18	€ 2,066,315.39	€ 3,963,168.06	€ 997,065.26	€ 2,115,460.19	€ 4,057,427.20
		Savings	€ 340,526.09	€ 724,346.94	€ 1,390,808.69	€ 317,363.01	€ 675,202.14	€ 1,296,549.56
	2020	Without Dapagliflozin	€ 917,776.68	€ 1,948,531.44	€ 3,738,321.15	€ 917,776.68	€ 1,948,531.44	€ 3,738,321.15
		With Dapagliflozin	€ 680,010.26	€ 1,442,768.79	€ 2,767,213.17	€ 696,183.48	€ 1,477,083.29	€ 2,833,027.97
		Savings	€ 237,766.42	€ 505,762.65	€ 971,107.98	€ 221,593.20	€ 471,448.15	€ 905,293.18
	2021	Without Dapagliflozin	€ 936,728.74	€ 1,988,768.55	€ 3,815,517.36	€ 936,728.74	€ 1,988,768.55	€ 3,815,517.36
		With Dapagliflozin	€ 694,052.45	€ 1,472,561.91	€ 2,824,356.03	€ 710,559.64	€ 1,507,585.01	€ 2,891,529.90
		Savings	€ 242,676.28	€ 516,206.64	€ 991,161.33	€ 226,169.09	€ 481,183.54	€ 923,987.45
Non-university Hospitals	2019	Without Dapagliflozin	€ 1,005,489.96	€ 2,134,755.49	€ 4,095,598.08	€ 1,005,489.96	€ 2,134,755.49	€ 4,095,598.08
		With Dapagliflozin	€ 744,999.86	€ 1,580,656.35	€ 3,031,679.86	€ 762,718.77	€ 1,618,250.34	€ 3,103,784.68
		Savings	€ 260,490.11	€ 554,099.14	€ 1,063,918.22	€ 242,771.19	€ 516,505.16	€ 991,813.40
	2020	Without Dapagliflozin	€ 758,760.16	€ 1,610,923.51	€ 3,090,609.33	€ 758,760.16	€ 1,610,923.51	€ 3,090,609.33
		With Dapagliflozin	€ 562,189.81	€ 1,192,790.69	€ 2,287,758.19	€ 575,560.81	€ 1,221,159.77	€ 2,342,169.74
		Savings	€ 196,570.35	€ 418,132.82	€ 802,851.13	€ 183,199.35	€ 389,763.75	€ 748,439.59
	2021	Without Dapagliflozin	€ 1,165,085.49	€ 2,473,592.72	€ 4,745,668.36	€ 1,165,085.49	€ 2,473,592.72	€ 4,745,668.36
		With Dapagliflozin	€ 863,249.32	€ 1,831,544.67	€ 3,512,880.64	€ 883,780.65	€ 1,875,105.73	€ 3,596,430.23
		Savings	€ 301,836.18	€ 642,048.05	€ 1,232,787.72	€ 281,304.84	€ 598,486.99	€ 1,149,238.13
HF Clinics	2019	Without Dapagliflozin	€ 127,326.19	€ 270,326.21	€ 518,629.65	€ 127,326.19	€ 270,326.21	€ 518,629.65
		With Dapagliflozin	€ 94,340.07	€ 200,160.08	€ 383,904.63	€ 96,583.83	€ 204,920.65	€ 393,035.33
		Savings	€ 32,986.12	€ 70,166.12	€ 134,725.02	€ 30,742.36	€ 65,405.56	€ 125,594.31

*Total cost of annual subsequent hospitalizations in patients that could have initiated dapagliflozin during the index-hospitalization due to heart failure.

^ΔThe scenario A considered a 26% expected RRR on HFHs. In the DAPA-HF & DELIVER pooled-analysis the reported RR associated with dapagliflozin for a first hHF and total HF hospitalizations were 26% and 29%, respectively. Therefore, to be cautious, we considered the value reported for the first hHF as an extrapolation for the projection of HFHs in our model, given that the reduction in HFHs-associated risk in the DAPA-HF and DELIVER pooled-analysis likely falls above 29%.

[†]The scenario B considered a 24% RRR as expected RRR on HFHs derived by weighting DAPA-HF and DELIVER RRRs with PORTHOS epidemiological data. HF, heart failure. HFHs, heart failure subsequent hospitalizations. RRR, relative risk reduction.

SUPPLEMENTARY DATA

Table S1: ICD-9 codes used for heart failure diagnosis.

ICD 9	Description
428	HF
428.0	Congestive HF, unspecified
428.1	Left HF
428.2	Systolic HF
428.20	Systolic HF, unspecified
428.21	Acute systolic HF
428.22	Chronic systolic HF
428.23	Acute on chronic systolic HF
428.3	Diastolic HF
428.30	Diastolic HF, unspecified
428.31	Acute diastolic HF
428.32	Chronic diastolic HF
428.33	Acute on chronic diastolic HF
428.4	Combined systolic and diastolic HF
428.40	Combined systolic and diastolic HF, unspecified
428.41	Acute combined systolic and diastolic HF
428.42	Chronic combined systolic and diastolic HF
428.43	Acute on chronic combined systolic and diastolic HF
428.9	HF, unspecified
402.11	Benign hypertensive heart disease with HF
404.01	Hypertensive heart and chronic kidney disease, malignant, with HF and with chronic kidney disease stage I – IV, or unspecified

404.03	Hypertensive heart and chronic kidney disease, malignant, with HF and with chronic kidney disease stage V or end stage renal disease
404.11	Hypertensive heart and chronic kidney disease, benign, with HF and with chronic kidney disease stage I – IV, or unspecified
404.13	Hypertensive heart and chronic kidney disease, benign, with HF and chronic kidney disease stage V or end stage renal disease
404.91	Hypertensive heart and chronic kidney disease, unspecified, with HF and with chronic kidney disease stage I – IV, or unspecified
404.93	Hypertensive heart and chronic kidney disease, unspecified, with HF and chronic kidney disease stage V or end stage renal diseases
785.51	Cardiogenic shock

Table S2: ICD-10 codes used for heart failure diagnosis.

ICD 10	Description
150	HF
I50.1	Left ventricular failure, unspecified
I50.2	Systolic (congestive) HF
I50.20	Unspecified systolic (congestive) HF
I50.21	Acute systolic (congestive) HF
I50.22	Chronic systolic (congestive) HF
I50.23	Acute on chronic systolic (congestive) HF
I50.3	Diastolic (congestive) HF
I50.30	Unspecified diastolic (congestive) HF
I50.31	Acute diastolic (congestive) HF
I50.32	Chronic diastolic (congestive) HF
I50.33	Acute on chronic diastolic (congestive) HF
I50.4	Combined systolic (congestive) and diastolic (congestive) HF
I50.40	Unspecified combined systolic (congestive) and diastolic (congestive) HF
I50.41	Acute combined systolic (congestive) and diastolic (congestive) HF
I50.42	Chronic combined systolic (congestive) and diastolic (congestive) HF

I50.43	Acute on chronic combined systolic (congestive) and diastolic (congestive) HF
I50.8	Other HF
I50.81	Right HF
I50.810	Right HF, unspecified
I50.811	Acute right HF
I50.812	Chronic right HF
I50.813	Acute on chronic right HF
I50.814	Right HF due to left HF
I50.82	Biventricular HF
I50.83	High output HF
I50.84	End stage HF
I50.89	Other HF
I50.9	HF, unspecified
I11.0	Hypertensive heart disease with HF
I13.0	Hypertensive heart and chronic kidney disease with HF and stage I – IV chronic kidney disease, or unspecified chronic kidney disease
I13.2	Hypertensive heart and chronic kidney disease with HF and with stage V chronic kidney disease, or end stage renal disease
R57.0	Cardiogenic shock

Table S3: Heart failure hospitalization costs according to Portuguese legislation.

Designation	Level of severity	Hospitalization price	Inpatient daily cost	Cost/day estimation
Heart Failure (HF)	1	€1,168.09	€584.05	€876.07
	2	€1,692.04	€846.02	€1,269.03
	3	€2,589.59	€863.20	€1,726.40
	4	€5,947.40	€1,189.48	€3,568.44

The cost/day estimation result from the average between the inpatient daily cost (which counts only with overnight costs) and hospitalization price (counts the maximum costs with the hospitalization, depending in other factors such as comorbidities,) reported in Portaria 207/2017 of the Portuguese legislation.

Table S4: Heart failure hospitalization costs according to Portuguese legislation.

Cost projection approach	Level of severity	Cost projection
Conservative	1	€876.07
Average	1,2,3,4	€1,859.98
Complex	4	€3,568.44

Levels of severity according to Portuguese legislation.

Table S5: Details of cost-saving projections.

Analysis	Expected HFHs risk reduction	Approach	Cost/day	HF hospitalized patients / year ^f	HF hospitalized patients eligible to DAPA / year ^g	Days of HF subsequent hospitalization ^h	Hospital without Dapagliflozin			Hospital with Dapagliflozin					
							Annual HF subsequent hospitalization rate ^a	HF subsequent hospitalizations / year	Total cost of annual subsequent hospitalizations	Annual HF subsequent hospitalization rate with dapagliflozin	HF subsequent hospitalizations / year	Daily Dapagliflozin Cost	Dapagliflozin treatment costs in hHF patients	Total cost of annual HF subsequent hospitalization	Savings in HF subsequent hospitalizations / year
Scenario A ^b	26%	Conservative	€876.07	a	$b = a \times (1 - 0.194)$	c	d	$e = d \times b$	$y = e \times c \times 876.07$	$f = (1 - 26\%) \times d$	$g = f \times b$	€1,10	$h = €1,10 \times e \times g$	$z = g \times c \times 876.07 + h$	$w = y - z$
		Average	€1,859.98	a	$b = a \times (1 - 0.194)$	c	d	$e = d \times b$	$y = e \times c \times 1,859.98$	$f = (1 - 26\%) \times d$	$g = f \times b$	€1,10	$h = €1,10 \times e \times g$	$z = g \times c \times 1,859.98 + h$	$w = y - z$
		Complex	€3,568.44	a	$b = a \times (1 - 0.194)$	c	d	$e = d \times b$	$y = e \times c \times 3,568.44$	$f = (1 - 26\%) \times d$	$g = f \times b$	€1,10	$h = €1,10 \times e \times g$	$z = g \times c \times 3,568.44 + h$	$w = y - z$
Scenario B ^c	24%	Conservative	€876.07	a	$b = a \times (1 - 0.194)$	c	d	$e = d \times b$	$y = e \times c \times 876.07$	$f = (1 - 24\%) \times d$	$g = f \times b$	€1,10	$h = €1,10 \times e \times g$	$z = g \times c \times 876.07 + h$	$w = y - z$
		Average	€1,859.98	a	$b = a \times (1 - 0.194)$	c	d	$e = d \times b$	$y = e \times c \times 1,859.98$	$f = (1 - 24\%) \times d$	$g = f \times b$	€1,10	$h = €1,10 \times e \times g$	$z = g \times c \times 1,859.98 + h$	$w = y - z$
		Complex	€3,568.44	a	$b = a \times (1 - 0.194)$	c	d	$e = d \times b$	$y = e \times c \times 3,568.44$	$f = (1 - 24\%) \times d$	$g = f \times b$	€1,10	$h = €1,10 \times e \times g$	$z = g \times c \times 3,568.44 + h$	$w = y - z$

^ΔThe scenario A considered a 26% expected RRR on HFHs. In the DAPA-HF & DELIVER pooled-analysis the reported RR associated with dapagliflozin for a first hHF and total HF hospitalizations were 26% and 29%, respectively. Therefore, to be cautious, we considered the value reported for the first hHF as an extrapolation for the projection of HFHs in our model, given that the reduction in HFHs-associated risk in the DAPA-HF and DELIVER pooled-analysis likely falls above 29%.

[†]The scenario B considered a 24% RRR as expected RRR on HFHs derived by weighting DAPA-HF and DELIVER RRRs with PORTHOS epidemiological data.

•Information obtained from the data collected by the authors.

▫To obtain the dapagliflozin eligible patients, we have taken in account the renal function. Specifically, 19% of HF patients were excluded assuming they wouldn't comply with renal requirements to start iSGTL2 according to eGFR > 30 ml/min/1.73m².

HF, heart failure. HFHs, heart failure subsequent hospitalizations. RRR, relative risk reduction

Table S6: Cost-saving projections for hospital readmissions associated with dapagliflozin use excluding the diabetic population.

		Total cost of annual subsequent hospitalization	SCENARIO A (26% expected RRR on HFHs ^Δ)			SCENARIO B (24% RRR derived by weighting DAPA-HF, DELIVER with PORTHOS study [†])		
			Conservative	Average	Complex	Conservative	Average	Complex
University Hospitals	2019	Without Dapagliflozin	€ 585,930.51	€ 1,243,988.92	€ 2,386,633.34	€ 585,930.51	€ 1,243,988.92	€ 2,386,633.34
		With Dapagliflozin	€ 434,134.76	€ 921,097.98	€ 1,766,654.85	€ 444,460.13	€ 943,005.18	€ 1,808,672.59
		Savings	€ 151,795.75	€ 322,890.93	€ 619,978.48	€ 141,470.38	€ 300,983.74	€ 577,960.75
	2020	Without Dapagliflozin	€ 408,786.39	€ 867,894.28	€ 1,665,083.49	€ 408,786.39	€ 867,894.28	€ 1,665,083.49
		With Dapagliflozin	€ 302,882.98	€ 642,622.82	€ 1,232,542.84	€ 310,086.69	€ 657,906.82	€ 1,261,857.37
		Savings	€ 105,903.40	€ 225,271.46	€ 432,540.65	€ 98,699.70	€ 209,987.45	€ 403,226.12

2021	Without Dapagliflozin	€ 417,227.81	€ 885,816.26	€ 1,699,467.41	€ 417,227.81	€ 885,816.26	€ 1,699,467.41	
	With Dapagliflozin	€ 309,137.51	€ 655,892.96	€ 1,257,994.81	€ 316,489.97	€ 671,492.58	€ 1,287,914.68	
	Savings	€ 108,090.31	€ 229,923.30	€ 441,472.60	€ 100,737.85	€ 214,323.69	€ 411,552.72	
Non-university Hospitals	2019	Without Dapagliflozin	€ 447,854.71	€ 950,840.23	€ 1,824,218.00	€ 447,854.71	€ 950,840.23	€ 1,824,218.00
		With Dapagliflozin	€ 331,829.96	€ 704,039.24	€ 1,350,338.80	€ 339,722.13	€ 720,783.96	€ 1,382,454.96
		Savings	€ 116,024.75	€ 246,800.98	€ 473,879.21	€ 108,132.58	€ 230,056.27	€ 441,763.04
	2020	Without Dapagliflozin	€ 337,958.93	€ 717,520.52	€ 1,376,586.54	€ 337,958.93	€ 717,520.52	€ 1,376,586.54
		With Dapagliflozin	€ 250,404.64	€ 531,280.22	€ 1,018,989.07	€ 256,360.21	€ 543,916.07	€ 1,043,224.49
		Savings	€ 87,554.29	€ 186,240.30	€ 357,597.47	€ 81,598.72	€ 173,604.45	€ 333,362.05
	2021	Without Dapagliflozin	€ 518,940.06	€ 1,101,761.52	€ 2,113,765.43	€ 518,940.06	€ 1,101,761.52	€ 2,113,765.43
		With Dapagliflozin	€ 384,499.39	€ 815,787.26	€ 1,564,670.16	€ 393,644.24	€ 835,189.77	€ 1,601,883.94
		Savings	€ 134,440.68	€ 285,974.26	€ 549,095.27	€ 125,295.83	€ 266,571.75	€ 511,881.50
HF Clinics	2019	Without Dapagliflozin	€ 56,712.29	€ 120,405.84	€ 231,002.54	€ 56,712.29	€ 120,405.84	€ 231,002.54
		With Dapagliflozin	€ 42,019.96	€ 89,153.19	€ 170,994.74	€ 43,019.35	€ 91,273.59	€ 175,061.64
		Savings	€ 14,692.33	€ 31,252.65	€ 60,007.79	€ 13,692.94	€ 29,132.25	€ 55,940.89

*Total cost of annual subsequent hospitalizations in patients that could have initiated dapagliflozin during the index-hospitalization due to heart failure.

^ΔThe scenario A considered a 26% expected RRR on HFHs. In the DAPA-HF & DELIVER pooled-analysis the reported RR associated with dapagliflozin for a first hHF and total HF hospitalizations were 26% and 29%, respectively. Therefore, to be cautious, we considered the value reported for the first hHF as an extrapolation for the projection of HFHs in our model, given that the reduction in HFHs-associated risk in the DAPA-HF and DELIVER pooled-analysis likely falls above 29%.

[†]The scenario B considered a 24% RRR as expected RRR on HFHs derived by weighting DAPA-HF and DELIVER RRRs with PORTHOS epidemiological data. HF, heart failure. HFHs, heart failure subsequent hospitalizations. RRR, relative risk reduction.