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Dapagliflozin: Improving heart failure outcomes does not necessarily mean increasing costs

Dapagliflozina: melhorar resultados na insuficiência cardíaca não significa aumentar custos

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Imagine a disease that is estimated to affect 16.5% of people aged 50 years old or older in Portugal (1). Now imagine that forecasts indicate that in Portugal, the prevalence of this disease will just keep rising in the coming years (2). Finally, imagine that following the diagnosis of this disease, patients are hospitalized, on average, once per year (3), and that even under conservative approach, the hospitalization-associated costs are 876 euros per/day in Portugal, and the average length of stay is 10 days (4). I am no economist or politician but seems like this disease could have a major economic impact and be a major challenge in the coming years. This disease is real, and is called heart failure (HF).

Heart failure hospitalizations are the major driver of HF costs, representing 39% of the total HF costs in Portugal (5). Any new therapy that can reduce mortality, reduce the burden of hospitalizations and improve the quality of life in this population could have a significant socioeconomic impact in the next years.

SGLT2 inhibitors are one of these game-changing therapies. Previous trials have shown that both dapagliflozin and empagliflozin could improve outcomes in HF patients, even in patients with HF with preserved ejection fraction (6), a subpopulation that comprises more than 90% of the Portuguese HF population (1). Prior to SGLT2 inhibitors, no prognosis-modifying therapy had been available (7). Accordingly, the European Society of Cardiology Guidelines endorsed a class of recommendation I, level of evidence A for all patients with HF irrespective of their ejection fraction (7). Cost-effectiveness studies in the United Kingdom, Germany and Spain have already

showed the incremental cost-effectiveness ratios in quality-adjusted life years for the use of dapagliflozin in HF (8).

Dulce Brito, Cândida Fonseca and Fátima Franco and the remaining team are to be congratulated on an important contribution to the evolving literature on the economic impact that dapagliflozin could have on the management of HF (4). In their well written, retrospective cohort evaluation, they collected data from two university hospitals, two non-university hospitals and two HF clinics between the years of 2019 and 2021, for the potential impact of in-hospital dapagliflozin initiation on healthcare costs related to HF readmissions.

Almost 5000 HF hospitalizations were registered in the enrolled hospitals between 2019 and 2021, with more than 80% of them as a first HF hospitalization. The baseline characteristics were well balanced between men and women (51% male) and the mean age of patients was78 years old, which is in accordance with the mean age of other registries (3).

The estimated cost per day of HF hospitalizations was determined in accordance with Portuguese legislation and the cost projection involved the use of three approaches (conservative, average and complex). In the conservative approach, the cost of a HF hospitalization was 876 euros per/day, in the average approach it was 1859 euros per/day and in the complex approach it was 3568 euros per/day, with an average length of stay for readmissions of 10 days (4).

The results involve a lot of figures, but even for clinicians, they are quite striking if we take into account the potential savings using dapagliflozin in this population.

In university hospitals, the use of dapagliflozin in the years studied could have saved 820 968 euros per hospital in a conservative approach. Considering that Portugal has seven university hospitals, savings could have reached more than five million euros over the period (4). In a complex approach, savings of 3 353 078 euros per hospital could have exceeded 23 million euros in total.

For non-university hospitals, an average cost reduction of 1 614 280 euros in the average approach per hospital could result in a potential total cost reduction of more than 48 million euros for all the 30 Portuguese non-university hospitals with a structured cardiology unit. These results considered a scenario with a 26% expected reduction in HF hospitalizations (4).

Even when considering an independent analysis excluding patients that could have previously taken or started an SGLT2 inhibitor, the results remain quite consistent regarding the potential reduction in costs when using dapagliflozin.

The authors point out some of the limitations of the study, especially regarding the low number of hospitals included in the analysis and the variability between them, the

impact of COVID-19 pandemia on the number of HF hospitalizations, which was more pronounced in the university hospitals (1242 in 2019, 844 in 2020 and 737 in 2021), that this data only represent the public National Health System and some statistical noise that may be caused by the assumptions made for this analysis.

However, the merits of this study by far outweigh the limitations. Conducting a study such as this is a step in the right direction for Portugal, as we are not collecting medical data as correctly or routinely as we should when compared with a country such as Denmark, for example. I commend the authors for gathering information from hospitals in different regions of Portugal and for dispelling the myth that such research cannot be conducted in our country. I would reinforce also that although the study was not intended to be a cost-effectiveness study, the results are well aligned with previous cost-effectiveness studies of dapagliflozin in the HF population (8).

As final remarks I would like to point out that it could be argued that this study assessed a cost-saving analysis utilizing just HF hospitalizations, yet these individuals might have SGLT2 inhibitor side effects, increasing the number of hospitalizations unrelated to HF. In fact, especially in the HF preserved ejection fraction population, HF-related hospitalizations were only 15% of the total number of hospitalizations in the DELIVER trial (6). However, looking at the total number of hospitalizations from any cause, this was also significantly reduced in the DELIVER trial by 11% (2226 vs. 2484) (9), with potential side effects of the SGLT2 inhibitors, such as hospitalizations caused by an infection being numerically lower (524 vs. 535) with dapagliflozin versus placebo. The potential of dapagliflozin to reduce the burden of hospitalizations for any reason in these populations is further supported by these results, and so the potential to reduce costs in this population.

Also, not only are SGLT2 inhibitors being under-prescribed, but they are able to improve clinical outcomes and reduce the HF economic burden. Mineralocorticoid receptor antagonists in HF with reduced ejection fraction are a classic example of an underused treatment, even though they reduced mortality by 15–30% and HF readmissions by up to 40% in landmark trials. European registries shows that less than 60% of HF patients with a formal indication for mineralocorticoid receptor antagonists are being prescribed them (10). When we consider that the cost of spironolactone in Portugal is only 1.33 euros per month for patients and 1.61 euros per month for the state co-payment, this becomes even less reasonable. We, as clinicians in this HF area, have room for improvement in the way we treat these patients.

In summary, this study demonstrates that new therapeutic tools are available to reduce the financial burden of HF. However, we should take note of the concerning 16.5% prevalence of HF in the Porthos study (1). Since HF with preserved ejection fraction

accounts for over 90% of cases (1), this should be a strong message that we need to rethink the HF problem in Portugal and that we are managing to diagnose this disease properly in most of the population.

Improving the primary care doctor's ability to identify HF prior to hospitalization is one potential course of action. To do so, they will need weapons that are not available at this point. Several strategies could facilitate this early diagnosis, including not only the co-payment of natriuretic peptides, but also the access to Doppler parameters for the diagnosis of HF with preserved ejection fraction.

Unfortunately, in Portugal, primary care physicians are still unable to ask for a Doppler echocardiography with co-payment for the patient, which is a pivotal exam in the diagnosis, management and treatment of HF.

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