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EDITORIAL

Implementing the treatment of heart failure with SGLT-2 inhibitors and sacubitril–valsartan: does money matter?

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This editorial refers to 'Dapagliflozin vs. sacubitril-valsartan for prevention of heart failure events in non-diabetic patients with reduced ejection fraction: a cost per outcome analysis', by R. Arbel *et al.*, doi: 10.1093/eurjpc/zwaa136.

The pandemic of heart failure (HF) represents a major global health problem with about 26 million people affected worldwide. Since HF occurs most commonly in elderly people, with almost one in three individuals aged ≥55 years developing this condition, the demographic imperative is immense. Over the last 30 years, the implementation of novel treatment strategies has resulted in significant improvement in HF outcome. As a result, the majority of patients experience a longer disease course leading to an increased prevalence of the disorder and to a heavy economic burden on the healthcare systems. Of note, in the USA and in Europe, the annual cost of care for this condition has been estimated to exceed 30 billion dollars, most of it spent on hospital care since every year about 1 million hospital admissions occur for HF.[1] On one hand, these data strengthen the importance of HF prevention mainly by tackling ischaemic heart disease and by vigorously treating hypertension, a frequent antecedent of HF. On the other hand, in light of the recent European approval of the first Sodium-Glucose coTransporter 2 (SGLT-2) inhibitor for the treatment of HF with reduced ejection fraction (HFrEF) in adults with and without type 2 diabetes, these data claim for cost-effectiveness studies before the inclusion of such novel drug class in clinical practice guidelines. However, in some countries, pharmaceutical companies do not need to perform a cost-effectiveness analysis for new drugs to gain market authorization and prices are negotiated between the statutory health insurance funds and the pharmaceutical companies.

In this scenario, the study by Arbel *et al.*[2] recently published in this journal provides an economic measure to compare the cost per outcome of using the SGLT-2 inhibitor, dapagliflozin, or the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril–valsartan for preventing HF events in non-diabetic patients with HFrEF. Extracting efficacy estimates from the non-diabetic cohorts of patients enrolled in DAPA-HF and PARADIGM-HF trials and considering the USA drug acquisition costs, the authors concluded that dapagliflozin and ARNI provide comparable value for money for preventing a composite outcome of cardiovascular death and hospitalization for HF. While dapagliflozin provides better value for money for the prevention of hospitalizations, ARNI provides better value for money for the prevention of all-cause and cardiovascular mortality. However, this type of analysis is sensitive to drug costs in each country.

The results of this study offer several points of discussion, some of which have been highlighted in *Table 1*. As first, beyond the comparison between ARNI and dapagliflozin, these data underscore the remarkable annual cost of pharmacological treatment for HF when compared to the median cost of an hospitalization (i.e. ∼150 000 dollars per year to prevent an hospitalization that costs 7000 dollars in the USA). While this difference is significantly mitigated in Europe because of the lower cost of the drugs (i.e. 9300 dollars per year to prevent an hospitalization that costs 4445 dollars in Germany), this consideration may raise concerns about the convenience of contemporary pharmacological treatment for HFrEF. In this regard, cost-effectiveness analyses provide a formal mechanism to establish whether the incremental cost of a new technology is justified by its health gains and associated cost offsets. However, the numbers provided by Arbel *et al.* do not represent a comprehensive cost-effectiveness evaluation because do not consider quality-adjusted life year (QALY) and the incremental cost-effectiveness ratios. QALY is the outcome of choice for most decision-making bodies as it accounts for both health-related quality of life and survival, and their changes, in a single metric. QALYs are obtained from generic preference-based measures to provide utility values, such as the EuroQol-5D, and these are multiplied by the duration lived in a health state. Preference-based measures describe health-related quality of life as a series of health states and then assign a utility weight

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Table 1 Sacubitril–valsartan and SGLT-2 inhibitors used as treatment for HFrEF irrespective of diabetes status: efficacy, safety, current recommendations, and economic measures

	Sacubitril-valsartan	SGLT-2 inhibitors[a]
NNT for HF events	21	20
NNT for CV death	31	74
NNT for hHF	36	23
NNT for all-cause death	36	64
Additional efficacy outcomes	—	• HbA1c ↓ 0.7–1.0% • 38% RRR of a composite kidney outcome ($P = 0.013$)[b]
Main side effects	Symptomatic hypotension, angio-oedema	Genito-urinary infections
Current European HF recommendations (2016)	Replacement for an ACE-I in ambulatory HFrEF patients who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker, and an MRA	Not included
Annual cost of the drug[b]		
Italy	1516€	672€
Germany	2400€	256€
UK	1099£	477£
QALY gain in Europe[b]	0.42–0.52 vs. enalapril	0.48–0.50 vs. standard of care
Incremental cost-effectiveness ratios per QALY gained[b]	17 100£ in UK 26 278€ in Germany	5822£ in UK 5379€ in Germany

ACE-I, angiotensin-converting enzyme inhibitors; CV, cardiovascular; HFrEF, heart failure with reduced ejection fraction; hHF, hospitalization for heart failure; MRA, mineralocorticoid receptor antagonist; NNT, number needed to treat; RRR, relative risk reduction.
[a]NNTs for SGLT-2 inhibitors derived from ref.[6]
[b]Defined as a composite of 50% or higher sustained decline in eGFR; end-stage renal disease (either sustained eGFR <15 mL/min, chronic dialysis or a renal transplantation); or renal death.
[b]For SGLT-2 inhibitors refers to dapagliflozin. Data derived from refs.[3–5]

to each health state on a common scale. In Europe, estimates of the QALYs gained with sacubitril/valsartan treatment compared with enalapril vary from 0.42 to 0.52 with incremental cost-effectiveness ratios ranging from 17 100 pounds to 26 278 euros per QALY gained in the UK and Germany, respectively.[3,4] Dapagliflozin compared to standard therapy conferred QALY gains of 0.48–0.50 with incremental cost-effectiveness ratios of 5822 pounds and 5379 euros per QALY gained in the UK and Germany, respectively.[5] Therefore, both ARNI and dapagliflozin are cost-effective but the more favourable incremental cost-effectiveness ratios of dapagliflozin reflect its lower cost compared to sacubitril/valsartan which, indeed, may decrease in 2023 after its patent expiration date. In general, we can assume that any treatment that can reduce mortality by 15–20% is likely to be cost-effective across a reasonable price range.

Second, the annual price of the two drugs, and therefore their cost needed to treat, is extremely different across the ocean. While in the USA the price of dapagliflozin is only 5% lower than ARNI, in the UK and in Germany it is about a half and one ninth of the ARNI price, respectively. Therefore, in two European countries dapagliflozin provides 2- to 10-fold better value for money compared to ARNI yielding an economic support to its incorporation in the update of European guidelines not only in addition but as an alternative to sacubitril–valsartan. Can we hypothesize an impact of this large difference in the value for money of dapagliflozin on American guidelines recommendations?

Third, an analysis of the comparative value for money of ARNI vs. SGLT-2 inhibitors prescribed in the setting of HFrEF should take into account additional outcomes. In patients with type 2 diabetes, chronic administration of SGLT-2 inhibitors improves glycaemic control generally reducing HbA1c by 0.7–1.0% and body weight by 3–4 kg. In addition, SGLT-2 inhibitors have clearly demonstrated renal benefits across the spectrum of kidney function.[6] Therefore, taking into account that diabetes, HF and chronic kidney disease often coexist,[7] the value of prescribing a single drug with multiple effects is even higher not only from an economic point of view but also for patients' compliance.

Finally, reported data from the contemporary DAPA-HF trial indicate that, despite initial excitement about sacubitril–valsartan that was approved in the USA and in Europe in 2015, the penetration of this drug is still modest. In the same line of evidence, real-world outpatient data demonstrated that only 13% of eligible outpatients with HFrEF were prescribed an ARNI in the USA, and of those treated, only 14% received target doses.[8] In Europe, ARNI prescription rates are higher but still do not exceed 25% of patients.[9] Part of the slow uptake may be explained by low rates of initiation among those hospitalized for HF. We can anticipate a similar phenomenon with SGLT-2 inhibitors. To date, prescription rates of this drug class by cardiologists are exceptionally low due to various reasons such as concerns with introducing confusion into the diabetes care plan,

unwillingness to take responsibility for diabetes management and lack of coordination of care with diabetologists.[10]

After many years of unsuccessful research efforts in the setting of HFrEF, the clear mortality benefit deriving from these two different drug classes represent a major opportunity to better the quality of care and should result in a large diffusion of these agents. Whether the combination of these therapies will result in additive benefit is still unclear. However, innovation is worthless if no one can afford it. Therefore, while healthcare systems need to find the delicate balance between accessibility and affordability, drug costs discrepancies should be minimized in order to offer the same standards of care across the world.

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