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The clinical and pharmacoeconomic impact of established and novel heart failure therapies

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Chronic heart failure (HF) is a prevalent condition associated with significant morbidity, mortality, and economic burden worldwide. The pharmacological management of HF has evolved over time with various drug classes demonstrating efficacy in improving patient outcomes. This review examines the pharmacoeconomic aspects of these therapies, including common and newer HF therapies as angiotensin receptor-neprilysin inhibitors, sodium–glucose co-transporter-2 inhibitors, iron supplementation, and vericiguat, a novel soluble guanylate cyclase stimulator. By analysing cost-effectiveness studies and their implications on healthcare resource utilization, this paper aims to inform clinicians and policymakers on HF management optimization from both clinical and economic perspectives.

Introduction

Heart failure (HF) affects ~65 million people globally, representing a growing public health problem and contributing to significant disability and mortality (*Figure 1*). The impact of the disease varies from patient to patient, but the overall burden is comparable to other disabling chronic conditions, with a significant reduction in quality of life.[1]

The management of HF has advanced significantly over the past few years, with pharmacotherapy playing a crucial role in improving survival and quality of life. However, the increasing prevalence of HF and the high costs associated with its treatment necessitate a thorough understanding of the pharmacoeconomic implications of these therapies.

The present review focuses on the pharmacoeconomics of the major drug classes used in HF management, including the recently approved ones.

Economic burden of chronic heart failure

The economic impact of HF is considerable. In the European Union (EU), cardiovascular diseases (including HF) account for €282 billion annually, distributed across different categories such as inpatient care, primary care, pharmaceuticals, informal care, etc.[2] In Italy, for example, the annual cost per capita purchasing power parity adjusted is estimated at around €726, in line with the EU mean value of €630. Regarding HF in Italy, in 2020, it accounted for costs up to €429 566 868, representing 2.1% of total national healthcare spending[3] (*Figure 2*). In the USA, the direct and indirect costs associated are projected to increase to $70 billion by 2030.[4]

Pharmacoeconomics aims to assess the cost and value of drugs and pharmaceutical therapies. It involves comparing the economic impact, effectiveness, and outcomes of different treatment options to determine the most cost-efficient choice for patients and healthcare systems. This discipline integrates both clinical and economic aspects, often employing analyses like:

- Cost-effectiveness analysis: compares costs per unit of health outcome (e.g. cost per life-year gained).
- Cost-utility analysis: uses quality-adjusted life years (QALYs) to incorporate both quantity and quality of life.
- Cost–benefit analysis: converts benefits into monetary terms to compare directly with costs.

These methods help determine the value of therapies relative to their costs,[5] informing resource allocation

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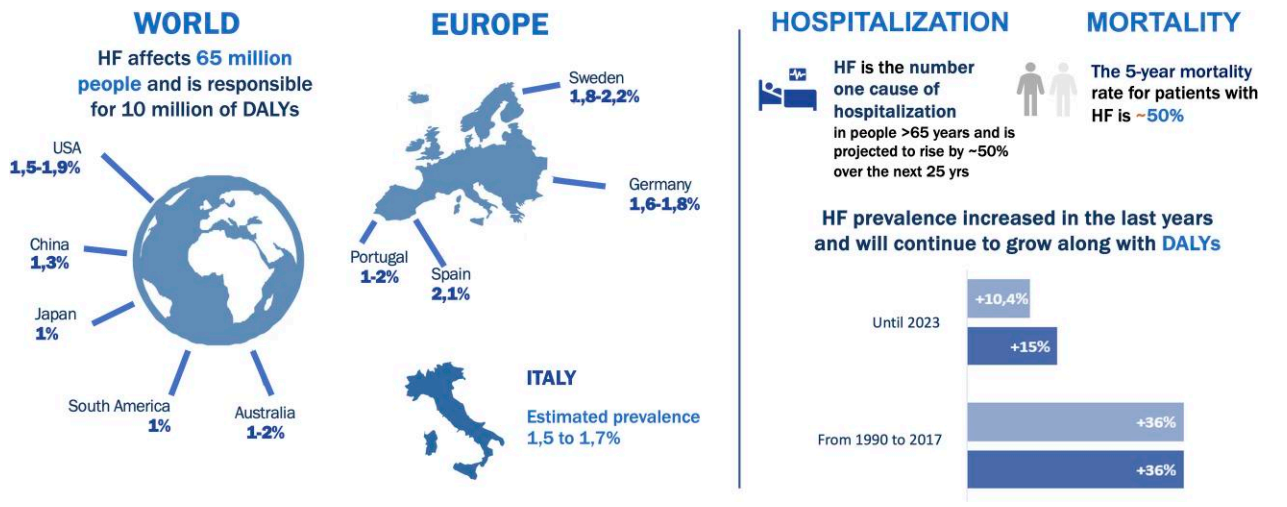

Figure 1 Epidemiological impact of heart failure. DALY, disability-adjusted life year.

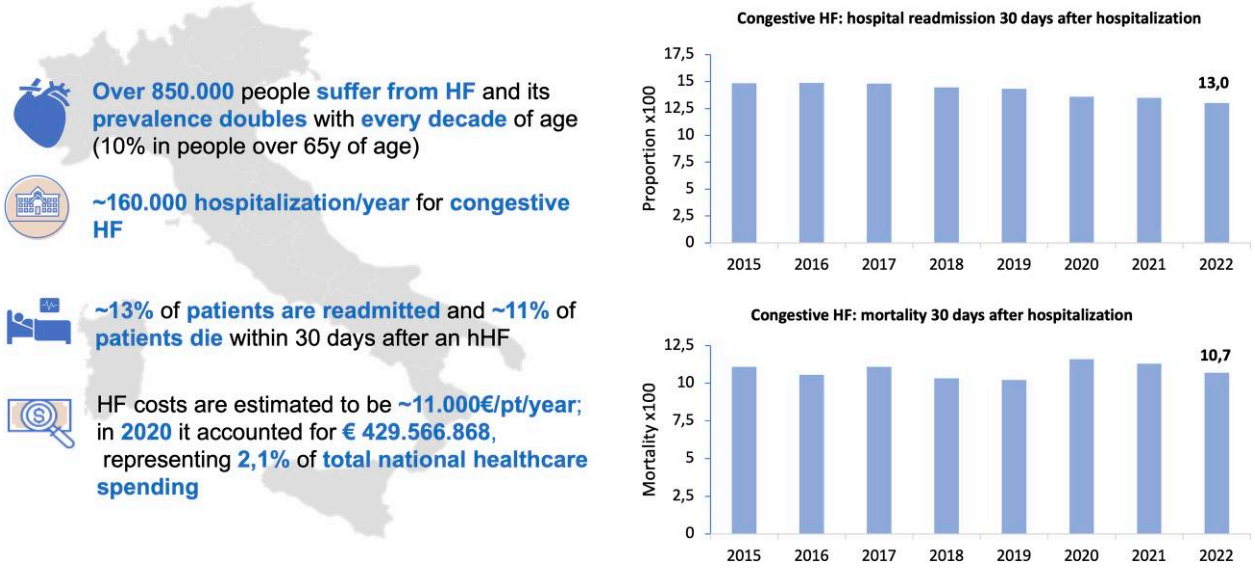

Figure 2 Incidence, outcome, and costs of heart failure in Italy.

decisions. In pharmacoeconomics, a pharmacological therapy is defined as 'cost-effective' when its ratio of costs to benefits is considered advantageous compared with available alternatives. In detail, cost-effectiveness evaluation is based on an analysis that considers both the costs associated with the therapy (direct costs, such as drugs, medical visits, hospitalizations, and indirect costs such as loss of productivity) and the clinical benefits, usually measured in terms of health outcomes like life years gained, QALY, or disability-adjusted life years (DALY). Cost-effectiveness analysis expresses the cost–benefit ratio as the incremental cost-effectiveness ratio (ICER). The result of the ICER is usually compared with a willingness-to-pay (WTP) threshold, which represents how much society is willing to spend to gain an improvement in one unit of health (e.g. one QALY). A therapy is considered cost-effective if the ICER is below the commonly accepted WTP threshold. If the ICER falls below this threshold, the therapy is judged to be a good investment in terms of costs and benefits for the healthcare system. With respect to EU, for example, €30 000–€50 000 per QALY is a reasonable average benchmark for general cost-effectiveness evaluations.[6]

Pharmacotherapy in chronic heart failure

The main drug classes which demonstrated significant improvement in terms of clinical outcomes in heart failure with reduced ejection fraction (HFrEF) are angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), angiotensin receptor-neprilysin inhibitors (ARNIs), sodium-glucose co-transporter-2 (SGLT2) inhibitors, soluble

guanylate cyclase (sGC) stimulator (vericiguat), and ferric carboxymaltose (FCM). Each class demonstrated clinical benefits, with varying impacts on mortality rates, hospitalization frequencies, and healthcare costs. ACEi, MRAs and BBs are well-established and undisputed cornerstones of HF therapy since the 1980 due to their ability to reduce mortality and hospitalizations. The cost of these molecules varies significantly, but overall has dropped considerably over the past few decades, making these drugs highly cost-effective in HFrEF.

Pharmacoeconomic evaluation of newer chronic heart failure therapies

Angiotensin receptor-neprilysin inhibitors

Sacubitril/valsartan, an ARNI, has become a cornerstone therapy in managing HFrEF. Its dual action, combining an angiotensin II receptor blocker (valsartan) with a neprilysin inhibitor (sacubitril), results in both the inhibition of the renin–angiotensin–aldosterone system and the augmentation of natriuretic peptides. In the PARADIGM-HF trial, sacubitril/valsartan reduced the risk of death from cardiovascular causes by 20% and decreased HF hospitalizations by 21% compared with enalapril.[7] Furthermore, patients on sacubitril/valsartan reported improved quality of life and functional status. It is now recommended as a Class I therapy for symptomatic HFrEF patients who remain symptomatic despite optimal therapy.[8] In a model-based analyses by Gaziano *et al.*,[9] it was founded that the health benefits associated with the use of sacubitril/valsartan in HFrEF patients with NYHA Class II–IV are cost-effective when compared with the use of enalapril at commonly accepted WTP thresholds of $50 000 per QALY gained. Moreover, sacubitril/valsartan reduces the risk of death and the need for implantable cardioverter-defibrillator (ICD) implantation, providing to be a more cost-effective strategy compared with the extensive use of ICDs, potentially lowering the costs associated with the procedure and device management.[10] Despite its proven efficacy and cost-effectiveness, barriers remain in the widespread implementation of sacubitril/valsartan, including prescription inertia and concerns about affordability, especially in lower-income settings. Physicians may be hesitant to switch stable patients from ACE inhibitors or ARBs to sacubitril/valsartan, and concerns about hypotension and renal function also influence prescribing behaviour.

Sodium-glucose co-transporter-2 inhibitors

Sodium–glucose co-transporter-2 inhibitors, such as dapagliflozin and empagliflozin, have transformed the management of HF with demonstrated benefits across the entire ejection fraction spectrum of heart failure (HFrEF, HFmrEF, and HFpEF). Initially developed as antidiabetic agents, SGLT2 inhibitors were found to exert a protective effect on the cardiovascular system, which has since been a subject of intense pharmacoeconomic analysis. The DAPA-HF[11] and EMPEROR-Reduced[12] trials demonstrated a significant reduction in hospitalizations for HF and cardiovascular mortality with dapagliflozin and empagliflozin, respectively. In economic analyses, both medications have been shown to be cost-effective due to their ability to reduce hospitalization rates. Hospitalization is a significant cost driver in HF, and the reduction in these events leads to considerable savings for healthcare systems. McEwan *et al.*[13] demonstrated that, either in the UK than in Spanish and German setting, treatment with dapagliflozin was estimated to increase significantly life years and QALYs (+0.58 and +0.48, respectively), and to reduce lifetime hospitalizations for HF (925 and 820 events per 1000 patients for placebo and dapagliflozin, respectively). These results were principally driven by reductions in cardiovascular and all-cause mortality, resulting in significant life-year and QALY gains for those patients with HFrEF treated with dapagliflozin. The avoidance of HF hospitalizations was associated with more modest QALY gains but contributed to important cost-savings, which partially offset the additional cost of dapagliflozin. In probabilistic sensitivity analyses performed by the authors, more than 90% of simulations were cost-effective at a WTP threshold of £20 000/QALY in UK and €20 000/QALY in Germany and Spain. Regarding empagliflozin, Tafazzoli *et al.*[14] developed a lifetime Markov cohort model and found that in the UK, Spain, and France, empagliflozin plus standard of care (SoC) yielded additional QALYs (0.19, 0.23, and 0.21) at higher cost (£1185, €1770, and €1183 per patient) than SoC alone, with incremental cost-effectiveness ratios of £6.152/QALY, €7.736/QALY, and €5.511/QALY, respectively. Reduced HF hospitalizations incidence provided most cost offsets for empagliflozin plus SoC. Probabilistic sensitivity results indicated that empagliflozin plus SoC remained cost-effective vs. SoC at WTP thresholds of £20 000/QALY, €20 000/QALY, and €30 000/QALY in 79.6, 75.5, and 97.3% of UK, Spain, and France model runs, respectively. Another analysis[15] showed that among HFmrEF and HFpEF patients (with patient-reported outcomes sourced from DELIVER trial),[16] it was predicted that dapagliflozin could increase QALYs by 0.231, with 91, 89, and 92% of simulations being cost-effective according to WTP thresholds in the UK, Germany, and Spain, respectively.

When comparing cost-effectiveness between dapagliflozin vs. empagliflozin, Nguyen *et al.*[17] reported that among three strategies (dapagliflozin-SoC, empagliflozin-SoC, and SoC), dapagliflozin-SoC was the most cost-effective strategy and dominated empagliflozin-SoC in an extended sense (at the WTP threshold of $100 000/QALY, dapagliflozin-SoC, empagliflozin-SoC, and SoC were cost-effective in 72.1, 20.8, and 7.1% of 1000 iterations, respectively). Of note, dapagliflozin-SoC was not cost-effective vs. empagliflozin-SoC in HFrEF patients with chronic kidney disease (CKD). These differences were mainly driven by the significant reduction in cardiovascular mortality with dapagliflozin, but not with empagliflozin, providing an added value in HFrEF patients.

Soluble guanylate cyclase stimulator (vericiguat)

Vericiguat is a newer agent in the management of HF, particularly targeting patients with worsening HF. As an sGC stimulator, it works by enhancing the nitric oxide signalling pathway. The VICTORIA trial demonstrated that vericiguat significantly reduced the composite endpoint of cardiovascular death or HF hospitalization compared with placebo, especially in high-risk HFrEF

patients.[18] Given its novelty, fewer pharmacoeconomic evaluations have been completed for vericiguat compared with ARNI and SGLT2 inhibitors. However, the available data suggest a positive pharmacoeconomic profile. Vericiguat's primary value lies in its use among patients who continue to deteriorate despite optimal medical therapy, offering an additional layer of protection against further hospitalizations.

Initial cost-effectiveness studies indicate that vericiguat, when added to standard therapy for patients with advanced HFrEF, can provide an acceptable ICER, particularly given the high cost burden associated with frequent hospitalizations in this patient group. Vericiguat's utility in reducing hospital readmissions is economically beneficial, given the substantial costs associated with repeat hospital stays for worsening HF. The estimated ICER for vericiguat vs. placebo (i.e. $66 509 per QALY gained in 2020 US dollars) places the cost-effectiveness of vericiguat at intermediate value, in the range of other recently approved therapies for the treatment of chronic HF in the outpatient setting. The drug would meet thresholds for a high value (i.e. ICER < $50 000 per QALY gained), at 50% of base-case pricing. However, attention should be paid to patient selection: in patients in the highest quartile of N-terminal pro-B-type natriuretic peptide {NT-proBNP, >5314 pg/mL; hazard ratio [HR] of all-cause death 1.14 [95% confidence interval (CI), 0.95–1.38], P=0.15}, there were 0.25 fewer estimated QALYs in the vericiguat compared with the placebo group (95% CI, −0.57 to 0.07). Thus, vericiguat is economically unattractive in the highest NT-proBNP quartile due to this clinically unfavourable scenario of shorter estimated life expectancy. The economic benefit of vericiguat may be therefore most pronounced in healthcare systems with high hospitalization costs, and in patients at high risk of recurrent hospitalizations, where the cost of the drug is offset by the decrease in healthcare utilization.

Ferric carboxymaltose

Another important target in HFrEF is iron deficiency, common among these patients and associated with an increased risk of hospitalization and reduced quality of life. Intravenous iron supplementation, particularly with FCM, has been shown to improve symptoms and reduce HF hospitalizations (up to 26% relative risk reduction).[19] Various pharmacoeconomic analyses have been conducted. In the Spanish analysis,[20] for example, FCM use was associated with cost-savings mostly determined by a reduced number of hospitalizations, resulting in an annual cost saving of €53 480 per patient. In the French analysis,[21] a base-case analysis, the modelled 5-year cost difference between the scenarios with FCM vs. no iron deficiency treatment in a population of 189 334 prevalent and incident patients led to €800 000 savings, mainly from a reduction in the hospitalization costs associated with worsening HF (-€35 800 000) as well as a reduction in the follow-up costs (-€2 900 000). However, when accounting for a two ambulatory session administration protocol, budget impact reached € + 36.9 m, thus eliminating cost-savings observed with the hypotetic first administration in the ambulatory setting and the second one during HF hospitalization.

Quadruple therapy

Considering optimized medical therapy, the analysis performed by Dixit *et al.*[22] showed that the treatment with quadruple therapy (BBs, MRA, ARNIs, and SGLT2i) in HFrEF resulted in 2.8 additional years of life compared with double therapy (BBs and ACEi) and 10 years survival rates were 50% for the quadruple therapy and 33% for the double therapy. Moreover, treatment with quadruple therapy increased also the QALY and lifetime cost compared with triple and double therapy: the incremental cost-effectiveness ratios of quadruple therapy vs. triple therapy and double therapy were $81 000 and $51 081, respectively, and in 91.7 and 99.9% of probabilistic simulations quadruple therapy had an ICER of <$150 000.

Conclusions

The management of chronic HF has evolved significantly with the introduction of newer pharmacologic agents such as sacubitril/valsartan, SGLT2 inhibitors, and vericiguat, which have improved clinical outcomes. Established therapies like ACE inhibitors, ARBs, BBs, and MRAs remain highly cost-effective in HFrEF, especially due to reduced drug prices over time, and they form the backbone of HF treatment. Newer agents, despite their higher initial costs, have demonstrated substantial benefits in reducing hospitalization rates—a key driver of HF costs.

The pharmacoeconomic analysis of chronic HFrEF drug therapies highlights that while newer agents such as sacubitril/valsartan, SGLT2 inhibitors, and vericiguat come at a higher cost, they deliver significant clinical benefits that translate into cost-effectiveness, particularly by decreasing hospitalization rates. These newer therapies, when integrated appropriately into clinical practice, can enhance both patient outcomes and economic efficiency. Barriers such as high drug costs, prescription inertia, and concerns over side effects remain challenges that need to be addressed to fully realize the benefits of these therapies. Policymakers and healthcare providers must work together to develop strategies that improve access to these effective treatments, particularly in settings with limited resources. Future research should continue to focus on real-world evidence of cost-effectiveness, integrating pharmacoeconomic considerations into clinical guidelines to ensure optimal management of HF, ultimately aiming for better resource allocation and improved long-term outcomes for HF patients.

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Data availability

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