Costs of care and financial hardship among patients with heart failure

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With the implementation of new therapies, more patients are living with heart failure (HF) as a chronic condition. Alongside these advances, out-of-pocket (OOP) medical costs have increased, and patients experience significant financial burden. Despite increasing interest in understanding and mitigating financial burdens, there is a relative paucity of data specific to HF. Here, we explore financial hardship in HF from the patient perspective, including estimated OOP costs for guideline-directed medical therapy for HF with reduced ejection fraction, hospitalizations, and total direct medical costs, as well as the consequences of high OOP costs. Studies estimate that high OOP costs are common in HF, and a large proportion are related to prescription drugs. Subsequently, the effects on patients can lead to worsening adherence, delayed care, and poor outcomes, leading to a financial toxicity spiral. Further, we summarize patients' cost preferences and outline future research that is needed to develop evidence-based solutions to reduce costs in HF. (Am Heart J 2024;269:94–107.)

With the implementation of new evidence-based therapies and treatments, more patients are living with heart failure (HF) as a chronic condition. In the United States (US), the most recent estimates suggest that over 6.2 million people have HF and that the prevalence is expected to rise by nearly 50% in 2030.[1,2] Along with increasing prevalence, healthcare expenditures for HF are expected to dramatically increase; total costs of HF were estimated at $30.7 billion in 2012 and are expected to increase by 127% to $69.8 billion by 2030.[1] The increase in total healthcare expenditures in HF are primarily driven by the costs of hospitalizations, however, outpatient care, including the use of novel pharmacotherapies, are contributing to an increasing proportion of overall costs.[2-5] Moreover, prior analyses suggest that this may be a conservative estimate and that when the costs of HF are assessed in the context of co-morbidities, the total estimated costs are quadrupled.[6] Unfortunately, along with the high societal costs of HF care, more financial burden is experienced directly by patients through out-of-pocket (OOP) costs, which is the focus of this scoping review. This financial hardship leads to a myriad of downstream consequences, including a range of economic, psychological, and potential physical harms, to patients and their families.

Foundational prior research initially among patients with cancer conceptualized the effect of high OOP costs with the term, "financial toxicity."[7] This encompasses the hardships from direct medical expenses, such as payments for medications, diagnostic testing, outpatient visits, and hospitalizations, as well as indirect costs, including parking, childcare, and medical travel.[7,8] The latter categories may be unexpected for patients and families, which further exacerbates the distress of the direct OOP medical expenses. Altogether, these circumstances exacerbate difficult decisions for patients and families, including having to decide between spending money on basic needs, such as housing, food, and household bills, and their medical expenses. Based on population-level research, these financial burdens are associated with delayed or forgone care leading to worse outcomes, including poor quality-of-life and mortality.[9,10] Further, at a national level, these concerns are intensifying. In a US poll from 2022, 38% of patients reported that they put off treatment due to costs, which is a nearly fifty percent increase from 2021.[11] These data add urgency to the need to understand the current state of financial hardship and identify opportunities for intervention.

Among patients with HF specifically, there is increasing interest in understanding and mitigating the phenomenon of financial hardship.[12-15] Unfortunately, there is a dearth of available data specific to HF and relatively few texts have synthesized the available evidence published to date. The aim of this scoping review is to

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synthesize the current knowledge of patient-level costs and financial hardship among patients with HF in the US and to identify areas of future research. To do this, we summarize the estimated OOP costs of guideline-directed medical therapy (GDMT) for HF with reduced ejection fraction (HFrEF) as well as the available costs of tafamidis for transthyretin cardiac amyloidosis. Next, the OOP costs related to hospitalizations and worsening HF events (WHFE) are examined along with the estimates of the total OOP costs for HF. With this context, the consequences of OOP costs and financial hardship in HF are described and we propose the concept of the "financial toxicity spiral." Finally, we briefly survey current and future opportunities to reduce financial burden among patients with HF and identify areas of future research.

Methods

We conducted a scoping review of published literature to characterize the OOP costs among patients with HF as well as to describe the current state of financial hardship and costs preferences in this population. A medical librarian with expertise in systematic searching partnered with the authors to compose a search mixing subject headings and keywords to represent the concepts of financial hardship and HF. Otherwise, the authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. No extramural funding was used to support this work.

Studies were limited to original research articles that were written in English language and included data on the OOP costs, financial hardship, or cost preferences of patients with HF. Data sources included self-reported surveys, single and multi-institution studies, as well as commercial insurance and Medicare claims. Literature searches were performed in MEDLINE, EMBASE, and SCOPUS databases. 78 titles and abstracts were reviewed against the selection criteria and the full-text of 50 articles were retrieved and reviewed for inclusion. Overall, 33 studies were identified and the flow chart is presented in accordance with PRISMA guidelines in Figure 1.[100]

Based on seminal work in oncology literature and with underlying principles grounded in economic theory,[7,16-18] Figure 2 provides a conceptual framework of financial toxicity in HF. The process starts with the clinical and social context of patients and their exposures, such as the costs of prescription drugs and hospitalizations. These clinical and social factors can be modified by the insurance status of a patient as well as health system practices and public policy. Together, these expose patients to financial hardship, which can result in distress, treatment nonadherence, and decisions to forego or delay care, and eventually, to worse health outcomes and quality-of-life.

OOP costs related to the treatment of heart failure

Patient-level costs of prescription drugs for heart failure

From 2005 to 2015, no new prescription drugs were approved for HF in the US, and the standard of care for the majority of patients was composed of low-cost generic medications. In the years since, novel pharmacotherapies have been approved, including sacubitril-valsartan, ivabradine, vericiguat, and sodium-glucose transport protein-2 (SGLT-2) inhibitors for HFrEF and tafamidis for transthyretin cardiac amyloidosis. Below, we overview the OOP costs among insured patients associated with GDMT for HFrEF (Table 1). These include both generic medications, such as mineralocorticoid receptor antagonists (MRA), beta-blockers (BB), and angiotensin-converting enzyme (ACE) inhibitors, and patented drugs, such as angiotensin receptor-neprilysin inhibitors (ARNI) and SGLT-2 inhibitors. Further, we briefly overview the available evidence regarding the OOP costs for ivabradine, vericiguat, hydralazine-isosorbide dinitrate (H-ISDN), and tafamidis.

Mineralocorticoid receptor antagonists

A pillar of treatment for HF for over 20 years, few recent studies have examined the OOP costs associated with MRAs. The average OOP cost of spironolac-

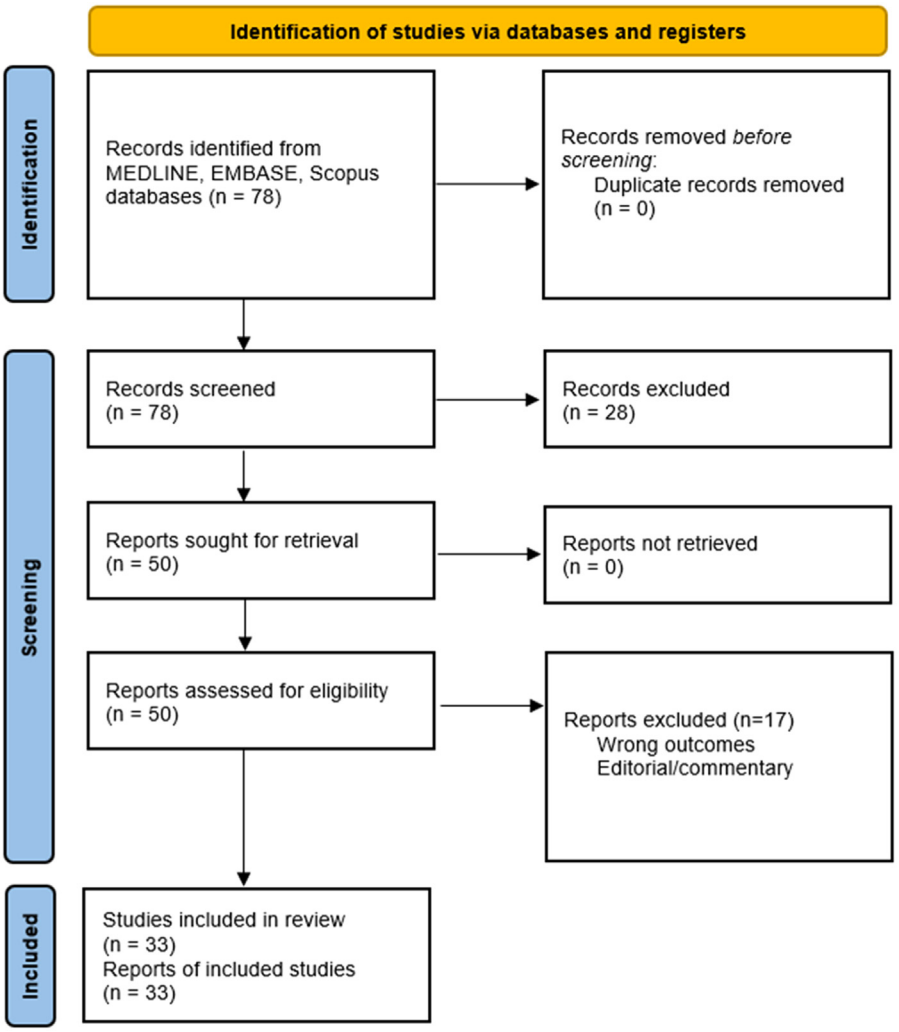
Table 1. Estimated out-of-pocket costs for 30-day supply of prescription drugs

	Medicare[19-23]	Commercial insurance[20,22]	Patient assistance program[24-29]
MRA	$1	-	-
ACE inhibitor	<$5	$7	-
BB	$1	-	-
ARNI	$42	$69	$10
SGLT-2 inhibitor	$42	$49	$10
Ivabradine		-	$20
Vericiguat		-	$10
H-ISDN		-	$25
Tafamidis		$250	$0

Estimates of Medicare Part D and commercial insurance out-of-pocket costs are reports as medians when available and means when not. For MRA, the out-of-pocket cost of spironolactone is reported in the table. The available estimate for out-of-pocket costs for tafamidis did not stratify by insurance type. No peer-reviewed estimates of out-of-pocket costs were available for ivabradine, vericiguat, and hydralazine-isosorbide dinitrate combination. Additionally, no peer-reviewed data reporting the out-of-pocket costs for MRA nor BB among commercially insured patients. Costs reported reflect different time points and payer estimates based on availability in the literature, which limits direct comparison across drugs. Finally, with regards to patient assistance programs, the lowest out-of-pocket cost available with assistance from the pharmaceutical company is reported.

ACE, angiotensin-converting enzyme inhibitor; *ARNI*, angiotensin receptor-neprilysin inhibitors; *BB*, beta blocker; *H-ISDN*, hydralazine-isosorbide dinitrate, *MRA*, mineralocorticoid receptor antagonist; *SGLT-2*, sodium glucose transport protein-2 inhibitor.

Figure 1



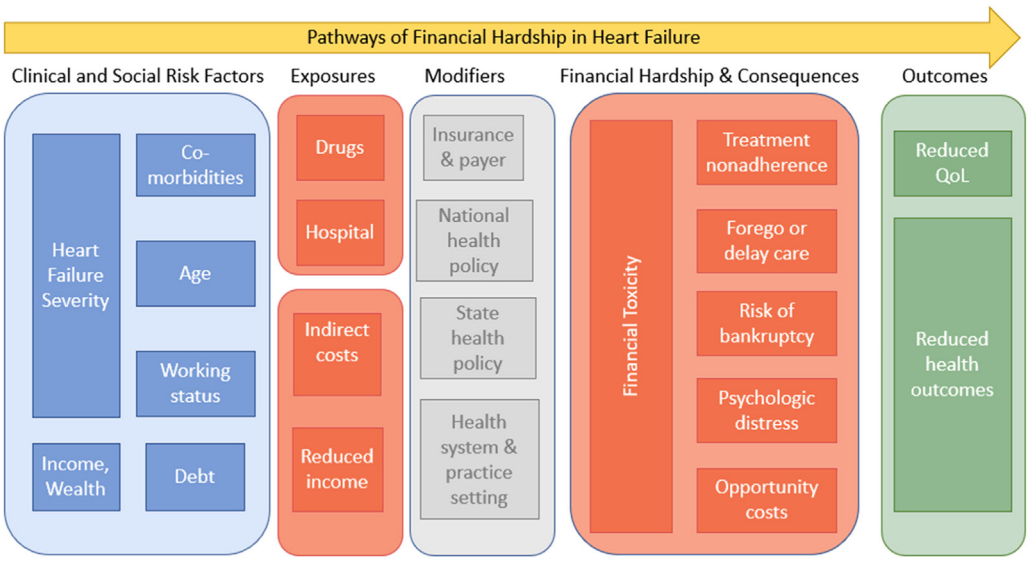
Flow diagram for identification and screening of included studies. *Studies were limited to original research articles that were written in English language and included data on the out-of-pocket costs, financial hardship, or cost preferences of patients with heart failure. Data sources included self-reported surveys, single and multi-institution studies, as well as commercial insurance and Medicare claims. Literature searches were performed in MEDLINE, EMBASE, and SCOPUS databases. Overall, 33 studies were identified.*

tone for a Medicare beneficiary for a 30-day prescription is $1 to $2.[19] Notably, this increases to $30 to $47 when eplerenone is used.[19] The effect of OOP costs of MRA on medication adherence and HF outcomes is not known.

Beta-blockers and ACE inhibitors

Additional long-standing medications used for HF, both ACE inhibitors and BB are relatively affordable. For ACE inhibitors, the average OOP cost to Medicare beneficiaries is <$5,[19] while the average OOP cost for commercially insured patients is $6.74 per month.[20] Evidence-based BB, which includes metoprolol succinate, carvedilol, and bisoprolol, are also available at a low cost, with average OOP costs of $1 for patients with Medicare coverage.[19] Historically, metoprolol succinate incurred the highest OOP costs for patients, this variation has largely resolved.[30] For example, a 30-day supply of metoprolol succinate can be purchased from an online pharmacy for $3.90 without any insurance coverage.[31] In a study with Medicare Part D enrollees with HF, OOP costs for a 30-day supply of BB amounted to 0.22% of their monthly income on average.[32] Despite the relatively low OOP costs, the proportion of total income

Figure 2



Pathways of financial hardship in heart failure. *QoL - quality of life; The clinical and social context of patients and their exposures, such as the costs of prescription drugs and hospitalizations, contribute to their financial hardship. These clinical and social factors can be modified by the insurance status of a patient as well as health system practices and public policy. Together, these expose patients to financial hardship, which can result in distress, treatment nonadherence, and delaying care.*

spent on a BB prescription was inversely associated with adherence.[32] These results are also supported by Patterson and colleagues, who demonstrate that patients with copayments for BB over $20 were less likely to adhere to the medication.[33]

In addition to medication adherence, several studies found that OOP costs of these medications are associated with hospitalizations. In an assessment of claims data from the early 2000s, Cole and colleagues found that an increase in copay by $10 per month for an ACE inhibitor predicted a 6.1% higher odds of HF-related hospitalization and the same increase in copay for a BB predicted 8.7% increased odds of hospitalization.[34] As a result, even in spite of the relative affordability of BB and ACE inhibitors, patients may be sensitive to the OOP costs.

Angiotensin receptor-neprilysin inhibitors (ARNI)

In the PARADIGM-HF trial, sacubitril-valsartan, which is the only ARNI available at this time, demonstrated over a 20% reduction in mortality and hospitalization compared to ACE inhibitors.[35] Recent guidelines synthesized available evidence that replacing ACE inhibitors with ARNI provides high economic value to system-level costs.[36] Despite robust evidence base, dissemination and implementation of the prescription drug remained low initially, with prescription rates ranging from 2-4% in the US during 2016 to 2018.[37] Economic factors, such as the prior authorization process and OOP costs may be limiting factors for broader dissemination.

The average OOP costs for sacubitril-valsartan are estimated to be between $42 and $57 per 30-day fill for Medicare beneficiaries[19,21] and $69 for patients with commercial insurance.[20] Depending on the timing of initiation and other healthcare costs by a patient, initiation can be quite expensive. In their analysis of Medicare beneficiaries, DeJong and colleagues found that the addition of sacubitril-valsartan to a standard HF medication regimen would lead to patients hitting their full $405 deductible in the first month of initiation and have an increase in OOP costs of $1594 annually.[21]

There are mixed data on the relationship between OOP costs and adherence to sacubitril-valsartan. Sangaralingham et al[38] showed that over one-third of patients were nonadherent to the medication and, of those, half discontinued the medication completely. While the reasons for discontinuation were not directly assessed, the study did not find any association between the magnitude of OOP costs and adherence.[38] One explanation may be that consistently high OOP costs across the majority of patients (ie, very few patients were paying less than $10 per month for the medication) limited the necessary variation needed to detect effects on adherence. This is supported by Mukhopadhay et al[39], who assessed the effect

of OOP costs of sacubitril-valsartan within a large, multisite health system. The authors analyzed the OOP costs with ordinal variables and found that patients with copayments over $10 had the highest odds of nonadherence even after accounting for demographic and clinical variables.[39] Among the patients with no copayment, the rate of nonadherence was 17.2% during the study period compared to 34.2% among patients with co-payment of over $100 ($P < .001$).[39]

SGLT-2 inhibitors

More recently, SGLT-2 inhibitors have been shown to reduce mortality and hospitalizations among patients with HFrEF.[40,41] Given the recency of their adoption, analysis of the OOP costs of SGLT-2 inhibitors is limited. Monthly patient-level OOP costs for SGLT-2 inhibitors varied based on insurance type. For those without insurance, the average costs per month were $138,[22] while for those with Medicare or commercial private insurance, the cost was $47[19] to $49[22] on average. A recent study evaluated a large cohort of patients with either type 2 diabetes or HF and found that adherence to the medication at 12-month varied by OOP costs.[42] Among patients with a co-payment of less than $10, 77% of them remained on the medication after 1 year.[42] Meanwhile, patients with large copayments had significantly reduced adherence even after adjusting for demographic, social, and clinical factors.[42] These data are limited as they were collected before adoption of SGLT-2 inhibitors in GDMT and do not differentiate between patients with HF and those with type 2 diabetes. To date, no work has assessed the effect of OOP costs on SGLT2 inhibitor adherence on HF outcomes since adoption into GDMT.

Quadruple therapy

When viewed together, the advent of new medications for HF has resulted in a significant increase in total OOP costs for patients. In their analysis, Zhou et al[43] estimated OOP costs for patients with HF in 2009 and in 2019. For the standard of care GDMT regimen in 2009, which consisted of medications available with generic formulations (MRA, ACE inhibitor, and BB), OOP costs dropped by 62% in 2019. On the other hand, when patients replaced the ACE inhibitor with ARNI therapy, an on patent drug, the current recommended treatment, the OOP costs nearly tripled (280%) in 2019 compared to 2009.[43] Their analysis did not include SGLT-2 inhibitors and it is challenging to forecast how the addition of this medication would affect an individual's total OOP costs given the variability of OOP maximums among insurance plans.

Among patients with Medicare, the estimated OOP costs for a regimen of BB, MRA, ARNI, and SGLT2 ranges from $2,217 annually[19] to as high as $2,849 annually.[23] Alternative regimens that replace the ARNI with an ACE inhibitor or exclude the SGLT-2 inhibitor have significantly lower annual costs at $1322 or $1319, respectively.[19] Moreover, regimens that only include BB, ACE inhibitor, & MRA resulted in even more dramatic reductions with annual OOP costs of $159[19] to $482.[23] In summary, for patients on quadruple therapy, the combined OOP costs of HF medications can be very high, averaging above $2,000 annually per patient.

Additional therapies for HFrEF

There is limited information on the OOP costs of H-ISDN, ivabradine, and vericiguat. This likely stems from more specific indications for use, including vericiguat in patients with worsening HF despite the use of GDMT and H-ISDN in patients who self-identify as Black or African American.[36] For vericiguat, no peer-reviewed evidence is available that characterizes OOP costs. Nonetheless, an online database of prescription drug prices estimates that monthly OOP costs range widely from $4 to $704.[44] Regarding, ivabradine, a recent study suggested that it is only covered by 26% of Medicare insurance plans even with prior authorization, thus fueling high OOP costs.[45] The case of H-ISDN is complicated by the use of a branded combination pill, which includes 2 generic drugs. Regarding total costs, the combination of the generic drugs is estimated to be less than a third of the costs of the combination pill.[46] For the branded combination H-ISDN, OOP costs are estimated to be as high as $486 per month, which presents a barrier to a large proportion of the target population.[47] Even through the pharmaceutical company's patient assistance program, the reduced OOP cost is $25 per prescription of branded H-ISDN for those who qualify.[27] With less than half of prescriptions of H-ISDN started in the hospital filled within 90 days of discharge,[48] it is possible that this discrepancy in affordability may present a barrier to access. Further, the lack of affordability of the combination pill spurred an increase in the use of off-label prescriptions of the generic drugs that make up H-ISDN.[49] While viewed as a practical solution, there is a lack of clear evidence supporting the practice, and available observational data suggest worse outcomes.[49,50] The high OOP costs of H-ISDN along with other GDMT further increase the barriers to care faced by racial minorities and may further exacerbate disparities in HF outcomes.

Importantly, these cost estimates are for HF-specific medications and may actually capture only a fraction of the total OOP prescription drug costs for a patient. For example, an analysis of a large cohort of Medicare patients found that 90% of OOP drug costs were related to co-morbidities rather than from HF-specific medications.[51] Additionally, the laboratory monitoring costs associated with the initiation and maintenance of these medications are not currently known. Finally, even though devices for HF, such as implantable cardioverter defibrillators (ICDs) and left ventricular assist devices

(LVADs), are associated with high costs,[3,52,53] their contribution to patient-level OOP costs is unknown.

Tafamidis

Tafamidis, which was approved in 2019, is a first-in-class medication that stabilizes transthyretin proteins and has been shown to reduce all-cause mortality and cardiovascular hospitalizations among patients with transthyretin cardiac amyloidosis.[54] The launch of the medication also was notable due to a list price of $225,000 and concerns over affordability for patients. While limited data is available on the financial burden associated with tafamidis, Masri and colleagues report their experience with prescribing and the use of payment assistance programs. In their reports, the majority of patients who were prescribed tafamidis received it (43 out of 50 patients), but more than half of these patients (28 patients) required financial assistance from either a foundation or from the manufacturer.[29] Among those without financial assistance the median and mean OOP costs for a 30-day supply were $250 and $1,683, respectively.[29] These findings are also supported by a recent letter-to-the-editor, which reports that even after copayment assistance from the manufacturer or other foundation, 30% of patients still had a monthly copayment greater than $1000.[55] There are no available data on the relationship between OOP costs for tafamidis and medication adherence or clinical outcomes nor the financial burden associated with these high direct costs.

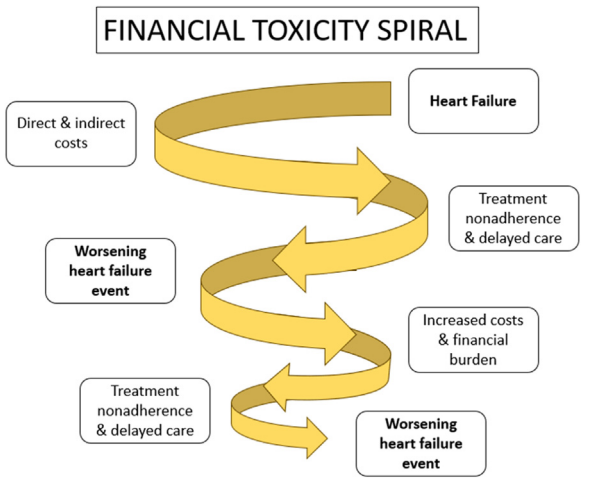
Hospitalizations, worsening heart failure events, and the "financial toxicity spiral"

While the high price tag of novel therapies for HF is substantial, the annual OOP costs associated with other direct medical expenses, including hospitalizations and insurance premiums, can be nearly triple the OOP costs for patients taking the most expensive medications available.[56] Further, OOP medication costs and the risk of hospitalization are intimately related. In a cohort of Medicare beneficiaries, McGee and colleagues demonstrated that the higher medication spending increased the frequency of hospitalizations for any reason and the total number of inpatient days.[57]

While hospitalizations and inpatient costs are the greatest contributor to the financial burden of HF on the health system,[58] the relative contribution of inpatient costs to total OOP costs is less than prescription drugs, insurance premiums, and outpatient visits for most patients with insurance.[56] Across families with at least 1 member with HF, the average total OOP costs for inpatient care and emergency visits in 1 year are estimated to be $185 and $39, respectively.[56] Interpretation of these data is limited because OOP costs of hospitalizations and emergency room visits likely vary depending on the time of year in which they occur and whether the patient has met their insurance deductible. Further, not every patient with HF experiences a hospitalization in a given year, and no direct estimates of the OOP costs of an HF hospitalization are available. As a result, the reported data of annual OOP costs for inpatient care and emergency visits likely underestimates the direct costs incurred by patients who receive such care in a given year. Moreover, the indirect costs of inpatient and emergency care, including lost wages, childcare costs, and caregiver support, are unknown.

Following a hospitalization or emergency room visit, patients may experience additional OOP costs. For example, WHFEs, which include hospitalizations and the use of intravenous diuretics, lead to increased intensity of care, including future hospitalizations and increased number of outpatient and emergency care visits.[59,60] At the same time, the OOP costs for medications following a WHFE also increase, with estimates as high as 50% on average for HF-specific prescriptions.[61] Consequently, this increases the risk of nonadherence and entry into the "financial toxicity spiral" (Figure 3). Among patients following a WHFE, nearly a fifth (18.4%) reported skip-

Figure 3



The financial toxicity spiral in heart failure. *The "financial toxicity spiral" in heart failure begins at diagnosis and initiation of treatment. Patients are exposed to direct costs, such as the costs of medications, and indirect costs, such as the cost of parking or travel to appointments. Later on, patients may experience an acute decompensation of heart failure, resulting an increased intensity of care. Along with increased care, out-of-pocket costs for prescription medications increase as high as 50%.[61] This increases the risk of financial hardship and associated treatment nonadherence and forgoing care. In turn, this spirals into another worsening heart failure event, augmenting the risk for financial toxicity even further.*

ping a dose of medications due to costs and 13.9% reported splitting pills due to costs.[61] Further, the financial stress may also lead to less adherence to HF self-care practices, including dietary regimens and delayed care.[62,63]

As illustrated in Figure 3, the "financial toxicity spiral" consists of high OOP costs, which may lead to worse adherence, increasing the risk of hospitalization. Hospitalizations and WHFE, in turn, lead to higher OOP prescription drug costs and increased risk of financial toxicity.

Examining the total OOP costs of heart failure

Direct costs

Of the data available, the estimated total direct OOP costs of HF appear to be over $4,000 annually. In their analysis of patients with private insurance, Piajariyakul et al[64] found that these costs ranged from $3,913 to $5,829 on average. Similarly, among a group of Medicare beneficiaries, the mean annual OOP costs was $4,423 (95% confidence interval, $3,908-$4,939), and the largest components of these costs were prescription medications and insurance premiums.[56] Notably, both of these estimates use data from records prior to the use of SGLT-2 inhibitors.

The relative contribution to OOP costs of drugs, hospitalizations, and insurance premiums differs based on the social and economic context of the patients. For example, prescription drug co-payments represented the largest category of health spending in 50% of low-income families, but only in 29% of middle- and high-income families.[56] Meanwhile, hospitalizations and inpatient costs were the most expensive OOP costs for those without insurance.[56]

Higher total direct OOP costs were associated with male sex, non-Hispanic White race/ethnicity, and the presence of diabetes mellitus as a co-comorbidity.[56] Klein et al[65] reported similar findings with increasing comorbidities and middle-to-high income associated with higher OOP expenses.

Indirect costs

While estimates of indirect costs related to HF at the societal level suggest a high contribution to total costs of care, the relative contribution of indirect costs to total OOP costs is not known.[2] Available data estimates that patients with HF spend $266 for medically-related travel annually.[64] Depending on the circumstances of the patient, additional indirect costs of HF may include lost wages due to hospitalizations and outpatient visits, which Korves et al[59] estimated to be approximately $1,800 per hospitalization.

Financial hardship and the consequences of high OOP costs

The high OOP costs described above manifest into burden and hardship on patients and their families. Wang et al[56] estimated that 1 in 7 families with a member with HF used greater than one-fifth of their postsubsistence income on medical expenses and that 5% of families used greater than 40% of their postsubsistence income on medical expenses. In a separate analysis, Ali et al[66] found that a third of patients with HF report financial hardship due to medical bills, and nearly 15% are unable to pay their bills at all. This results in the dangerous "financial toxicity spiral," including medication nonadherence, poor HF self-care practices, delayed care, and eventually increased risk of HF exacerbation and hospitalizations.

The burden of costs does not affect all patients equally. In their analysis of catastrophic burden, which is the threshold considered to be financially ruinous based on internationally accepted definitions, Wang and colleagues found that low-income families experienced 3x the rate of high financial burden (24% vs 8%) and 10x the rate of catastrophic burden (10% vs 1%) compared to middle- and high-income families.[56] Moreover, after adjusting for risk factors and comorbidities, low-income families were found to have 14-fold greater odds of catastrophic burden.[56] While the absolute total OOP costs may be higher in middle to high-income patients, the relative burden is greater among lower-income patients as well as patients who are younger, have less education, or identify as non-Hispanic Black race/ethnicity.[56,66,67]

The relative burden of financial hardship also manifests as an issue of health equity. In their analysis of the use of GDMT in Black, Hispanic, and American-Indian populations, Ilonze et al[68] found that financial strain plays a role in the relative underutilization of GDMT in these patient groups. The authors note that patients who identify as racial or ethnic minorities face greater barriers to access health insurance and prescription drugs.[68] These disparities are further compounded by differences in OOP costs at the end of life.[69] With newer GDMT and higher co-payments, the disparities observed in HF outcomes may worsen.

Finally, while the focus of this review is primarily on patients in the US, it is important to note, that HF-related financial hardship occurs globally, with similar descriptions in Canada,[70] Nigeria,[71,72] India,[73] and Australia among others.[74,75] The diversity in health systems and payment models, including countries with public payer options, limits the availability of direct comparisons. Further, data on financial hardship can be even more limited in other regions of the world. In a recent review of global financial hardship from OOP costs in cancer patients, the majority of evidence was from high-income countries

and less data was available from low-and-middle income countries.[76]

Interrupting the financial toxicity spiral

Patient engagement and cost communication in heart failure

The burden of high costs for GDMT and hospitalizations places many patients in difficult situations where they may forgo or delay necessary medical care or face catastrophic economic burden. To continue to deliver high-quality care, the patient's social and economic context should be considered along with their clinical context at the center of medical decision-making. Previous work has shown that patients with HF are open to cost conversations in clinical settings,[77] regardless of financial burden,[78] and prefer to have the conversations initiated by physicians.[78] Patients who had cost conversations rate their experience as generally positive,[78] and previous pilot projects have suggested the potential to promote health equity.[69] Despite this, half of patients with HF reported never having a medication-related cost discussions previously and only about 1 in 5 patients report having a physician-initiated conversation in the past year.[78,79]

While patients prefer to have cost discussions in clinical settings, there are barriers that may lead to their underutilization. As demonstrated in other medical conditions, clinicians may be hesitant to discuss patients' financial concerns if they are uncertain of the OOP costs incurred by the patient or if they lack time or awareness of resources.[80,81] In HF specifically, the lack of point-in-time estimates of OOP costs of individual patients is a critical barrier.[82,83] A recent study showed that even when physicians have access to the insurance information for patients, only about half were able to accurately estimate the OOP costs for their patients.[84] The challenge of cost discussions in clinical settings is further complicated by the need to contextualize OOP cost information within the HF prognosis, comorbidities, insurance status, personal financial situation, and values of an individual patient.

Decision aids and visualizations may be effective tools to approach cost discussions among patients with HF.[85,86] Recent research has shown that the use of a decision aid, which combines both the benefits of a new medications, such as an ARNI, alongside the perceived burdens of costs for patients, is feasible in a clinical setting.[77] While these tools offer the opportunity to better align care with patient preference and values, this means that for some patients, the cost of taking the drug outweigh the benefits. For example, in their evaluation of a decision aid for sacubitril-valsartan, Dickert et al[77] asked patients how much they would be willing to pay for the ARNI and found that the average was $50 a month. This is notably lower than the average OOP costs of ARNI among patients with commercial insurance.[20] With this in mind, only 5% of interviewed patients reported that they would definitely switch to an ARNI from an ACE inhibitor or angiotensin receptor blocker.[77] In a separate analysis, 92% of patients said they would definitely or probably switch to an ARNI if their physician recommended it and OOP costs were only $5 more per month than their current medication.[79] Of course, these preferences are not stagnant and instead depend on patient's clinical and socioeconomic context.[87] In their analysis, Dunbar and colleagues found that the amount patients were willing to pay in monthly OOP costs tripled among those who experienced a WHFE compared to those who did not ($75 vs $25).[61] These findings point to the need for continued patient engagement around their economic experiences with HF treatment as well as the complexity of doing so within the constraints of current clinical contexts and in ways that align with patient preferences and values.

Current and future opportunities to reduce financial burden in heart failure

Within the current system, a variety of methods have been implemented to reduce the OOP costs of patients with HF. The primary focus has been on prescription drug costs, and interventions have included both those initiated by patients, such as requesting generic medications, signing up for patient assistance, and programs, or those initiated by providers, such as co-payment vouchers. In their analysis, Dunbar et al[61] found that the most common action taken by patients with HF to reduce OOP prescription costs included purchasing 90-day supplies (61.1%), requesting generic alternatives (47.5%), and signing up for patient-assistance programs (31.2%). Another strategy for patients is to price shop among multiple pharmacies as service fees can vary significantly.[70,88] Resources like GoodRx and Cost Plus Drugs can help patients without insurance find more affordable options. Unfortunately, for those with insurance, the costs of GDMT in these programs are typically more expensive than the average OOP costs.[15]

Use of co-payment vouchers that reduce the OOP costs of prescription drugs to medicine is a common strategy for clinicians when prescribing expensive cardiovascular medications.[89] In an analysis of cost conversations when starting sacubitril-valsartan, 59% of physicians used free samples to facilitate initiation.[90] Another example from outside of HF is the ARTEMIS trial, which randomized hospitals to give patients who had a myocardial infarction a co-payment voucher for P2Y12 inhibitor or usual care. The authors found that co-payment assistance increased the persistence of therapy at 1 year (87.0% vs 83.8%, $P < .001$) and that greater OOP costs were associated with higher utilization of the co-payment vouchers.[91,92] Despite the difference in adherence to therapy, no difference was observed in clinical outcomes at 1

year.[92] With regards to prescription drugs for HF, Warden et al[93] found that through patient assistance programs and copayment cards, patients' co-payment for SGLT-2 inhibitors can be minimized, which resulted in only 4.3% of patients discontinuing the medication due to costs in their single institution practice. In the case of SGLT-2 inhibitors, patients with commercial insurance can also apply to the manufacturers for assistance, such as the case with the Boehringer Ingelheim Cares Foundation and empagliflozin (Jardiance).[28]

Despite the common use and the effectiveness of co-payment programs and patient assistance programs, there are several significant limitations. First, many patients may be unaware of programs or the application process may be difficult to navigate without support.[13,94] Application processes can include requirements to submit pay stubs, tax returns and verification of citizenship.[94] Further, co-payment vouchers are only available to those with private insurance, excluding patients with Medicare Part D and those without insurance. While the programs or vouchers can temporarily alleviate OOP costs, the relief is often inconsistent and does not include a mechanism for affordability after the initial eligibility period. Finally, these programs do not address the underlying causes that contribute to high costs of care.

National policy changes offer the opportunity to alleviate OOP costs by increasing the coverage for prescription drugs. The most notable recent policy in this arena is the Inflation Reduction Act of 2022, which addresses OOP costs for Medicare beneficiaries. First, beginning in 2025, OOP spending will be capped at $2,000 annually. When applied to patients with HFrEF who are on quadruple therapy, this is expected to lead to significant cost savings at the patient-level, ranging from $659 to $1349 annually.[23] Second, the legislation also removes the requirement for Medicare beneficiaries to pay 5% co-insurance in the catastrophic phase. Finally, the policy establishes the Medicare Drug Price Negotiation Program, which allows Medicare to negotiate directly with drug companies. Of the ten drugs selected for negotiation, 3 drugs, Entresto (sacubitril-valsartan), Jardiance (empagliflozin), and Farxiga (dapagliflozin), are used in the treatment of HF, underscoring the significant financial burden of these medications.[95] Negotiations with participating companies will occur over the next year and negotiated prices will become effective in 2026. Another area of opportunity within national health policy is to facilitate enrollment in the Medicare Part D Low-Income Subsidy program, which provides cost-sharing assistance to Part D enrollees with low incomes and modest assets. The promise of the program has been limited by suboptimal enrollment rates among eligible patients and may benefit from abbreviated enrollment processes or presumptive eligibility.[96] Legislation represents a promising step toward addressing the high costs of prescription medications.

While both policy and system level innovations have the capability to alleviate the burden of OOP costs on patients with HF,[15,97] there is also agency for clinicians to continue to meaningfully contribute as well. One area is the use of cost communication and shared decision-making when discussing OOP costs for HF. Shared decision-making is a collaborative strategy that partners clinicians and patients to work together on treatment decisions in order to align the decisions with patient preferences and goals.[98] When shared decision-making also includes conversations about costs, patients are afforded the opportunity to learn about the effects of a new treatment on their lives. Despite the potential benefit, use of shared decision-making may not always be effective. For example, in a recent trial that randomized patients with atrial fibrillation to a shared decision-making intervention or to usual care, increased clinician satisfaction and patient involvement in the decision-making process were reported in the intervention arm, but there were no differences in treatment rates.[99]

To more effectively incorporate cost communication and shared decision-making into clinical practice, solutions are needed to overcome existing barriers. For example, point-of-care price transparency tools should be integrated into electronic health records along with clinician support tools, such as alerts for patients at high-risk for financial hardship to discuss costs. Additionally, the development of robust, evidence-based decision aids may facilitate these complex conversations and shared decision-making. Finally, guidelines on how best to accurately represent the benefits and risks of various components of therapy, including factors such as treatment effectiveness and quality-of-life, should be developed to support the decision-making process.

Financial navigation and case management planning is another key piece to facilitate cost decisions, including assistance with picking the best insurance plan and applying to payment assistance programs. In clinical settings, the responsibility to assist in these areas is often unclear and can fall to desk staff, case managers, and clinicians, leaving patients with fragmented support. Importantly, this is also an opportunity for interdisciplinary collaboration. In their review of strategies to reduce OOP costs of patients with HF who live in Canada, McIntyre et al[70] focused on the collaboration between patients, prescribers, and pharmacists. Incorporating a larger role for pharmacists in outpatient HF practices has the potential to assist patients with financial navigation as well as prior authorizations, which may allow providers more time to conduct cost conversations with their patients.

Future directions

As novel drugs are developed for HF that reduce mortality and improve quality-of-life, it is imperative to understand the effects of OOP costs on financial hardship and clinical outcomes. The high OOP of new medications incorporated into routine HF practice may make patients more vulnerable to the risk of financial hardship. To this end, research is needed in a few key areas. First, the majority of research available regarding the OOP costs of prescription drugs comes from the Medicare population, and future research should examine patients under the age of 65. Additionally, future research would benefit from the collection of clinical characteristics in addition to the details of individual insurance plans, including OOP maximums. Specific populations of patients with HF, such as those with preserved ejection fraction or patients that undergo other specialized treatments, such as in cardio-oncology or oncology, or patients with ICDs or LVADs, should be evaluated further. Second, currently, only sparse data are available on the effect of the high OOP costs of SGLT-2 inhibitors on adherence, quality-of-life, and financial hardship. Third, additional research is needed to evaluate the indirect costs associated with HF treatment, such as the costs of parking and travel for medical appointments. Further, understanding the relative contribution of direct and indirect costs to total patient-level expenses across both ambulatory and hospital settings would help better inform the cost expectations of patients and their providers. Fourth, research is needed that examines the implementation and real-world use of cost conversations among HF patients in busy clinical settings as well as their ultimate effects on treatment decisions. Looking forward, when evaluating new potential treatments, studies should assess patient-centered costs in addition to patient-centered clinical benefits to inform future shared decision-making conversations.

Limitations

Key limitations of existing studies include the reliance on data from Medicare population, the inability to categorize HF as reduced or preserved ejection fraction in the majority of included studies, and the paucity of data on the direct OOP costs of ambulatory care, hospitalizations, and emergency room visits. Further research is needed to better characterize financial hardship in HF with particular focus on specific sub-populations of patients with HF (such as HF with preserved ejection fraction) as well as the direct OOP costs of hospitalizations and indirect costs associated with the disease.

Conclusion

High OOP costs are common in patients with HF and direct costs average over $4,000 annually. Moreover, OOP costs differ based on individual clinical, social, and economic factors. Based on the preliminary studies in this area, the financial burden on patients with HF and their families can initiate a "financial toxicity spiral," including worsening medication nonadherence, poor HF self-care practices, delayed care, and eventually increased risk of HF exacerbation and hospitalizations. With growing recognition of the role of financial hardship in quality-of-life and the ability to adhere to prescribed medication regimens, future patient-centered studies in HF are needed.

Conflicts of Interest

Dr Robert J. Mentz received research support and honoraria from Abbott, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Fast BioMedical, Gilead, Innolife, Eli Lilly, Medtronic, Medable, Merck, Novartis, Novo Nordisk, Pharmacosmos, Relypsa, Respicardia, Roche, Sanofi, Vifor, Windtree Therapeutics, and Zoll.

CRediT authorship contribution statement

Alexander H. Gunn: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Haider J. Warraich:** Writing – review & editing, Data curation. **Robert J. Mentz:** Conceptualization, Methodology, Data curation, Writing – review & editing, Supervision.

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References

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2023 Update: a report from the American Heart Association. Circulation 2023;147:e93–e621. doi:10.1161/cir.0000000000001123.
2. Bozkurt B, Ahmad T, Alexander KM, et al. Heart failure epidemiology and outcomes statistics: a report of the heart failure society of America. J Card Fail 2023;29:1412–51. doi:10.1016/j.cardfail.2023.07.006.
3. Heidenreich PA, Fonarow GC, Opsha Y, et al. Economic issues in heart failure in the United States. J Card Fail 2022;28:453–66. doi:10.1016/j.cardfail.2021.12.017.
4. Echouffo-Tcheugui JB, Bishu KG, Fonarow GC, Egede LE. Trends in health care expenditure among US adults with heart failure: the Medical Expenditure Panel Survey 2002-2011. Am Heart J 2017;186:63–72. doi:10.1016/j.ahj.2017.01.003.
5. Bhatnagar R, Fonarow GC, Heidenreich PA, Ziaeian B. Expenditure on heart failure in the United States: The Medical Expenditure Panel Survey 2009-2018. JACC Heart Fail 2022;10:571–80. doi:10.1016/j.jchf.2022.05.006.

6. Voigt J, Sasha John M, Taylor A, et al. A reevaluation of the costs of heart failure and its implications for allocation of health resources in the United States. Clin Cardiol 2014;37:312–21. doi:10.1002/clc.22260.
7. Zafar SY, Abernethy AP. Financial toxicity, Part I: a new name for a growing problem. Oncology (Williston Park) 2013;27:149 80-1.
8. Ubel PA, Abernethy AP, Zafar SY. Full disclosure–out-of-pocket costs as side effects. N Engl J Med 2013;369:1484–6. doi:10.1056/NEJMp1306826.
9. Tran G, Zafar SY. Price of cancer care and its tax on quality of life. J Oncol Pract 2018;14:69–71. doi:10.1200/JOP.2017.028498.
10. Ramsey SD, Bansal A, Fedorenko CR, et al. Financial insolvency as a risk factor for early mortality among patients with cancer. J Clin Oncol 2016;34:980–6. doi:10.1200/JCO.2015.64.6620.
11. M. Brenan, *Record High in U.S. Put Off Medical Care Due to Cost in 2022. The Gallup Poll* https://news.gallup.com/poll/468053/record-high-put-off-medical-care-due-cost-2022.aspx. [accessed 5 July 2023].
12. Clark KAA, Defilippis EM, Morris AA. Breaking the bank: the financial burden of living with heart failure. J Card Fail 2022;28:1434–6. doi:10.1016/j.cardfail.2022.07.004.
13. Slavin SD, Khera R, Zafar SY, et al. Financial burden, distress, and toxicity in cardiovascular disease. Am Heart J 2021;238:75–84. doi:10.1016/j.ahj.2021.04.011.
14. Whellan DJ, Psotka MA. Expenditure on heart failure in the united states: a rising tide lifts all boats. JACC Heart Fail 2022;10:581–2. doi:10.1016/j.jchf.2022.06.003.
15. Sukumar S, Wasfy JH, Januzzi JL, et al. Financial toxicity of medical management of heart failure: JACC review topic of the week. J Am Coll Cardiol 2023;81:2043–55. doi:10.1016/j.jacc.2023.03.402.
16. Pisu M, Martin MY. Financial toxicity: a common problem affecting patient care and health. Nat Rev Dis Primers 2022;8:7. doi:10.1038/s41572-022-00341-1.
17. Jones SM, Henrikson NB, Panattoni L, et al. A theoretical model of financial burden after cancer diagnosis. Future Oncol 2020;16:3095–105. doi:10.2217/fon-2020-0547.
18. Grossman M. On the concept of health capital and the demand for health. J Pol Econ 1972;80:223–55.
19. Faridi KF, Dayoub EJ, Ross JS, et al. Medicare coverage and out-of-pocket costs of quadruple drug therapy for heart failure. J Am Coll Cardiol 2022;79:2516–25. doi:10.1016/j.jacc.2022.04.031.
20. Shore S, Basu T, Kamdar N, et al. Use and out-of-pocket cost of sacubitril-valsartan in patients with heart failure. J Am Heart Assoc 2022;11:e023950. doi:10.1161/JAHA.121.023950.
21. DeJong C, Kazi DS, Dudley RA, et al. Assessment of national coverage and out-of-pocket costs for sacubitril/valsartan under Medicare Part D. JAMA Cardiol 2019;4:828–30. doi:10.1001/jamacardio.2019.2223.
22. Aggarwal R, Vaduganathan M, Chiu N, Bhatt DL. Out-of-pocket costs for SGLT-2 (Sodium-Glucose Transport Protein-2) inhibitors in the United States. Circ Heart Fail 2022;15:e009099. doi:10.1161/CIRCHEARTFAILURE.121.009099.
23. Johnson M, Nayak RK, Gilstrap L, Dusetzina SB. Estimation of out-of-pocket costs for guideline-directed medical therapy for heart failure under Medicare Part D and the inflation reduction act. JAMA Cardiol 2023;8:299–301. doi:10.1001/jamacardio.2022.5033.
24. Novartis. Entresto offers savings and support from the start; 2023.
25. Merck & Co. The Merck Access Program: Co-Pay Coupon for Verquvo; 2023.
26. Amgen Safety Net Foundation: Corlanor. https://www.corlanorhcp.com/patient-support
27. BiDil: Patient Savings & Support. 2023. https://www.bidil.com/patient-savings-support [accessed 5 July 2023].
28. Boehringer Ingelheim Patient Assistance Program. 2023. https://www.boehringer-ingelheim.com/us/our-responsibility/patient-assistance-program [accessed 5 July 2023].
29. Masri A, Chen H, Wong C, et al. Initial experience prescribing commercial tafamidis, the most expensive cardiac medication in history. JAMA Cardiol 2020;5:1066–7. doi:10.1001/jamacardio.2020.1738.
30. Hong M, Shcherbakova N. Comparison of discounted and undiscounted cash prices for cardiovascular medications by type of US community pharmacy. J Gen Intern Med 2021;36:114–20. doi:10.1007/s11606-020-06149-7.
31. Metoprolol Extended Release (ER), (Generic for Toprol XL), 2023, Mark Cuban CostPlus Drugs Company; Dallas, TX https://costplusdrugs.com/medications/metoprololextendedreleaseer-25mg-tablet/. [accessed 5 July 2023].
32. McGee BT, Phillips V, Higgins MK, Butler J. Prescription drug spending and medication adherence among Medicare beneficiaries with heart failure. J Manag Care Spec Pharm 2019;25:705–13. doi:10.18553/jmcp.2019.25.6.705.
33. Patterson ME, Blalock SJ, Smith AJ, Murray MD. Associations between prescription copayment levels and β-blocker medication adherence in commercially insured heart failure patients 50 years and older. Clin Ther 2011;33:608–16. doi:10.1016/j.clinthera.2011.04.022.
34. Cole JA, Norman H, Weatherby LB, Walker AM. Drug copayment and adherence in chronic heart failure: effect on cost and outcomes. Pharmacotherapy 2006;26:1157–64. doi:10.1592/phco.26.8.1157.
35. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004. doi:10.1056/NEJMoa1409077.
36. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022;79:1757–80. doi:10.1016/j.jacc.2021.12.011.
37. Gilstrap L, King A, Tomlin S, Austin AM. Variation in early diffusion of sacubitril/valsartan and implications for understanding novel drug diffusion. Am J Manag Care 2021;27:524–30. doi:10.37765/ajmc.2021.88791.
38. Sangaralingham LR, Sangaralingham SJ, Shah ND, et al. Adoption of Sacubitril/Valsartan for the Management of Patients With Heart Failure. Circ Heart Fail 2018;11:e004302. doi:10.1161/CIRCHEARTFAILURE.117.004302.
39. Mukhopadhyay A, Adhikari S, Li X, et al. Association between copayment amount and filling of medications for angiotensin receptor neprilysin inhibitors in patients with heart failure. J Am

Heart Assoc 2022;11:e027662. doi:10.1161/JAHA.122.027662.
40. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413–24. doi:10.1056/NEJMoa2022190.
41. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008. doi:10.1056/NEJMoa1911303.
42. Essien UR, Singh B, Swabe G, et al. Association of prescription co-payment with adherence to glucagon-like peptide-1 receptor agonist and sodium-glucose cotransporter-2 inhibitor therapies in patients with heart failure and diabetes. JAMA Netw Open 2023;6:e2316290. doi:10.1001/jamanetworkopen.2023.16290.
43. Zhou T, Liu P, Dhruva SS, et al. Assessment of hypothetical out-of-pocket costs of guideline-recommended medications for the treatment of older adults with multiple chronic conditions, 2009 and 2019. JAMA Intern Med 2022;182:185–95. doi:10.1001/jamainternmed.2021.7457.
44. Kittleson MM. Vericiguat in HFrEF: insights from the GWTG-HF registry. JACC Heart Fail 2023;11:224–6. doi:10.1016/j.jchf.2022.11.019.
45. Naci H, Kyriopoulos I, Feldman WB, et al. Coverage of new drugs in Medicare part D. Milbank Q 2022;100:562–88. doi:10.1111/1468-0009.12565.
46. Sacks CA, Lee CC, Kesselheim AS, Avorn J. Medicare spending on brand-name combination medications vs their generic constituents. JAMA 2018;320:650–6.
47. Hawkins-Taylor C, Carlson AM. Communication strategies must be tailored to a medication's targeted population: lessons from the case of BiDil. Am Health Drug Benefits 2013;6:401.
48. Khazanie P, Liang L, Curtis LH, et al. Clinical effectiveness of hydralazine-isosorbide dinitrate therapy in patients with heart failure and reduced ejection fraction: findings from the get with the guidelines-heart failure registry. Circ Heart Fail 2016;9:e002444. doi:10.1161/circheartfailure.115.002444.
49. Ofili E, Anand I, Williams RA, et al. Fixed-dose versus off-label combination of isosorbide dinitrate plus hydralazine hydrochloride: retrospective propensity-matched analysis in black medicare patients with heart failure. Adv Ther 2017;34:1976–88. doi:10.1007/s12325-017-0584-x.
50. Cole RT, Kalogeropoulos AP, Georgiopoulou VV, et al. Hydralazine and isosorbide dinitrate in heart failure: historical perspective, mechanisms, and future directions. Circulation 2011;123:2414–22. doi:10.1161/circulationaha.110.012781.
51. Fendrick AM, Djatche L, Pulungan Z, et al. Out-of-pocket payments for part d covered medications by Medicare fee-for-service beneficiaries with heart failure with reduced ejection fraction. Am Heart J 2022;246:74–81. doi:10.1016/j.ahj.2021.10.189.
52. Baras Shreibati J, Goldhaber-Fiebert JD, Banerjee D, et al. Cost-effectiveness of left ventricular assist devices in ambulatory patients with advanced heart failure. JACC: Heart Fail 2017;5:110–19.
53. Tomini F, Prinzen F, van Asselt A. A review of economic evaluation models for cardiac resynchronization therapy with implantable cardioverter defibrillators in patients with heart failure. Eur J Health Econ 2016;17:1159–72.
54. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007–16. doi:10.1056/NEJMoa1805689.
55. Cuddy SAM, Coyle ML, Falk RH. Initial monthly cost of tafamidis-the real price for patients. JAMA Cardiol 2020;5:847–8. doi:10.1001/jamacardio.2020.0863.
56. Wang SY, Valero-Elizondo J, Ali HJ, et al. Out-of-Pocket annual health expenditures and financial toxicity from healthcare costs in patients with heart failure in the United States. J Am Heart Assoc 2021;10:e022164. doi:10.1161/JAHA.121.022164.
57. McGee BT, Higgins MK, Phillips V, Butler J. Prescription drug spending and hospital use among Medicare beneficiaries with heart failure. Res Social Adm Pharm 2020;16: 1452–1458. doi:10.1016/j.sapharm.2019.12.019.
58. Osenenko KM, Kuti E, Deighton AM, et al. Burden of hospitalization for heart failure in the United States: a systematic literature review. J Managed Care Special Pharm 2022;28:157–67. doi:10.18553/jmcp.2022.28.2.157.
59. Korves C, Eldar-Lissai A, McHale J, et al. Resource utilization and costs following hospitalization of patients with chronic heart failure in the US. J Med Econ 2012;15:925–37. doi:10.3111/13696998.2012.685136.
60. Butler J, Djatche LM, Sawhney B, et al. Clinical and economic burden of chronic heart failure and reduced ejection fraction following a worsening heart failure event. Advances in Therapy 2020;37:4015–32. doi:10.1007/s12325-020-01456-1.
61. Dunbar SB, Tan X, Lautsch D, et al. Patient-centered Outcomes in HFrEF following a worsening heart failure event: a survey analysis. J Card Fail 2021;27:877–87. doi:10.1016/j.cardfail.2021.05.017.
62. Dickens C, Dickson VV, Piano MR. Perceived stress among patients with heart failure who have low socioeconomic status: a mixed-methods study. J Cardiovasc Nurs 2019;34:E1–8. doi:10.1097/jcn.0000000000000562.
63. Thomas A, Valero-Elizondo J, Khera R, et al. Forgone medical care associated with increased health care costs among the U.S. Heart Failure Population. JACC: Heart Fail 2021;9:710–19. doi:10.1016/j.jchf.2021.05.010.
64. Piamjariyakul U, Yadrich DM, Russell C, et al. Patients' annual income adequacy, insurance premiums and out-of-pocket expenses related to heart failure care. Heart Lung 2014;43:469–75. doi:10.1016/j.hrtlng.2014.05.013.
65. Klein S, Jiang S, Morey JR, et al. Estimated Health care utilization and expenditures in individuals with heart failure from the medical expenditure panel survey. Circ Heart Fail 2021;14:e007763. doi:10.1161/CIRCHEARTFAILURE.120.007763.
66. Ali HR, Valero-Elizondo J, Wang SY, et al. Subjective financial hardship due to medical bills among patients with heart failure in the United States: The 2014-2018 medical expenditure panel survey. J Card Fail 2022;28:1424–33. doi:10.1016/j.cardfail.2022.06.009.
67. Osborn CY, Kripalani S, Goggins KM, et al. Financial strain is associated with medication nonadherence and worse self-rated health among cardiovascular patients. J Health Care Poor Underserved 2017;28:499–513. doi:10.1353/hpu.2017.0036.
68. Ilonze O, Free K, Breathett K. Unequitable heart failure therapy for Black, Hispanic and American-Indian patients. Card Fail Rev 2022;8:e25. doi:10.15420/cfr.2022.02.

69. Piamjariyakul U, Smith CE, Werkowitch M, et al. Designing and testing an end-of-life discussion intervention for African American patients with heart failure and their families. J Hosp Palliat Nurs 2016;18:528–35. doi:10.1097/NJH.0000000000000290.
70. McIntyre WF, Belesiotis P, McClure GR, et al. Strategies to reduce out-of-pocket medication Costs for Canadians living with heart failure. Cardiovasc Drugs Ther 2021;35:1009–23. doi:10.1007/s10557-020-07046-1.
71. Ogah OS, Stewart S, Onwujekwe OE, et al. Economic burden of heart failure: investigating outpatient and inpatient costs in Abeokuta, Southwest Nigeria. PLoS One 2014;9:e113032. doi:10.1371/journal.pone.0113032.
72. Adeniji F. Burden of out-of-pocket payments among patients with cardiovascular disease in public and private hospitals in Ibadan, South West, Nigeria: a cross-sectional study. BMJ Open 2021;11:e044044. doi:10.1136/bmjopen-2020-044044.
73. Harikrishnan S, Ganapathi S, Reethu S, et al. Assessment of the impact of heart failure on household economic well-being: a protocol. Wellcome Open Res 2021;6:167. doi:10.12688/wellcomeopenres.16709.2.
74. Schönfeld S, Denhaerynck K, Berben L, et al. Prevalence and correlates of cost-related medication nonadherence to immunosuppressive drugs after heart transplantation: the international multicenter cross-sectional bright study. J Cardiovasc Nurs 2020;35:519–29. doi:10.1097/JCN.0000000000000683.
75. Oliveira Campinas A, Costa RC, Dias De Frias ADF, et al. Pill burden and out-of-pocket medication costs of a contemporary heart failure with reduced ejection fraction cohort. Eur Heart J 2021;42:778. doi:10.1093/eurheartj/ehab724.0778.
76. Ehsan AN, Wu CA, Minasian A, et al. Financial toxicity among patients with breast cancer worldwide: a systematic review and meta-analysis. JAMA Network Open 2023;6:e2255388. doi:10.1001/jamanetworkopen.2022.55388.
77. Dickert NW, Mitchell AR, Venechuk GE, et al. Show me the money: patients' perspectives on a decision aid for sacubitril/valsartan addressing out-of-pocket cost. Circ Cardiovasc Qual Outcomes 2020;13:e007070. doi:10.1161/CIRCOUTCOMES.120.007070.
78. Rao BR, Dickert NW, Morris AA, et al. Heart failure and shared decision-making: patients open to medication-related cost discussions. Circ Heart Fail 2020;13:e007094. doi:10.1161/CIRCHEARTFAILURE.120.007094.
79. Smith GH, Shore S, Allen LA, et al. Discussing out-of-pocket costs with patients: shared decision making for sacubitril-valsartan in heart failure. J Am Heart Assoc 2019;8:e010635. doi:10.1161/JAHA.118.010635.
80. Jagsi R, Ward KC, Abrahamse PH, et al. Unmet need for clinician engagement regarding financial toxicity after diagnosis of breast cancer. Cancer 2018;124:3668–76. doi:10.1002/cncr.31532.
81. Warsame R, Kennedy CC, Kumbamu A, et al. Conversations about financial issues in routine oncology practices: a multicenter study. J Oncol Pract 2019;15:e690–703. doi:10.1200/JOP.18.00618.
82. Allen LA, Teerlink JR, Gottlieb SS, et al. Heart failure spending function: an investment framework for sequencing and intensification of guideline-directed medical therapies. Circ Heart Fail 2022;15:e008594. doi:10.1161/CIRCHEARTFAILURE.121.008594.
83. Warraich HJ, Ali HJR, Nasir K. Financial toxicity with cardiovascular disease management: a balancing act for patients. Circ Cardiovasc Qual Outcomes 2020;13:e007449. doi:10.1161/CIRCOUTCOMES.120.007449.
84. Sloan CE, Millo L, Gutterman S, Ubel PA. Accuracy of physician estimates of out-of-pocket costs for medication filling. JAMA Netw Open 2021;4:e2133188. doi:10.1001/jamanetworkopen.2021.33188.
85. Thomson MC, Allen LA, Halpern SD, et al. Framing benefits in decision aids: effects of varying contextualizing statements on decisions about sacubitril-valsartan for heart failure. MDM Policy Pract 2021;6:23814683211041623. doi:10.1177/23814683211041623.
86. Venechuk GE, Allen LA, Doermann Byrd K, et al. Conflicting perspectives on the value of neprilysin inhibition in heart failure revealed during development of a decision aid focusing on patient costs for sacubitril/valsartan. Circ Cardiovasc Qual Outcomes 2020;13:e006255. doi:10.1161/circoutcomes.119.006255.
87. Audureau E, Davis B, Besson MH, et al. Willingness to pay for medical treatments in chronic diseases: a multicountry survey of patients and physicians. J Comp Eff Res 2019;8:357–69. doi:10.2217/cer-2018-0106.
88. Hauptman PJ, Goff ZD, Vidic A, et al. Variability in retail pricing of generic drugs for heart failure. JAMA Inter Med 2017;177:126–8. doi:10.1001/jamainternmed.2016.6955.
89. Kang S-Y, Sen AP, Levy JF, et al. Factors associated with manufacturer drug coupon use at US pharmacies. JAMA Health Forum 2021;2:e212123. doi:10.1001/jamahealthforum.2021.2123.
90. Akrobetu D, Dickert N, Nguyen T-V, et al. Impact of out-of-pocket cost discussions on sacubitril/valsartan clinical decision during physician-patient interactions. J Am Coll Cardiol 2021;77:627. doi:10.1016/S0735-1097(21)01986-0.
91. Fanaroff AC, Peterson ED, Kaltenbach LA, et al. Agreement and accuracy of medication persistence identified by patient self-report vs pharmacy fill: a secondary analysis of the cluster randomized ARTEMIS trial. JAMA Cardiol 2020;5:532–9. doi:10.1001/jamacardio.2020.0125.
92. Wang TY, Kaltenbach LA, Cannon CP, et al. Effect of medication co-payment vouchers on P2Y12 inhibitor use and major adverse cardiovascular events among patients with myocardial infarction: the ARTEMIS randomized clinical trial. JAMA 2019;321:44–55. doi:10.1001/jama.2018.19791.
93. Warden BA, Purnell JQ, Duell PB, et al. Real-world utilization of pharmacotherapy with new evidence-based cardiovascular indications in an academic preventive cardiology practice. Am J Prev Cardiol 2021;5:100144. doi:10.1016/j.ajpc.2020.100144.
94. Zafar SY, Peppercorn JM. Patient financial assistance programs: a path to affordability or a barrier to accessible cancer care? J Clin Oncol 2017;35:2113–16. doi:10.1200/jco.2016.71.7280.
95. Medicare drug price negotiation program: selected drugs for initial price applicability year 2026. 2023. *Medicare Drug Price Negotiation Program*. https://www.cms.gov/files/document/fact-sheet-medicare-selected-drug-negotiation-list-ipay-2026.pdf [accessed 5 September 2023].
96. Roberts ET, Glynn A, Donohue JM, Sabik LM. The Relationship between take-up of prescription drug subsidies and Medicaid

among low-income Medicare beneficiaries. J Gen Intern Med 2021;36:2873–6. doi:10.1007/s11606-020-06241-y.
97. Hung C-L, Chao T-F, Su C-H, et al. Income level and outcomes in patients with heart failure with universal health coverage. Heart 2021;107:208–16. doi:10.1136/heartjnl-2020-316793.
98. Hong YR, Salloum RG, Yadav S, et al. Patient-provider discussion about cancer treatment costs and out-of-pocket spending: implications for shared decision making in cancer care. Value Health 2020;23:1592–8. doi:10.1016/j.jval.2020.08.002.
99. Kunneman M, Branda ME, Hargraves IG, et al. Assessment of shared decision-making for stroke prevention in patients with atrial fibrillation: a randomized clinical trial. JAMA Inter Med 2020;180:1215–24. doi:10.1001/jamainternmed.2020.2908.
100. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160. doi:10.1136/bmj.n160.