Circulation: Heart Failure

ADVANCES IN HEART FAILURE, MECHANICAL CIRCULATORY SUPPORT AND TRANSPLANT

Heart Failure Spending Function: An Investment Framework for Sequencing and Intensification of Guideline-Directed Medical Therapies

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ABSTRACT: Heart failure with reduced ejection fraction is managed with increasing numbers of guideline-directed medical therapies (GDMT). Benefits tend to be additive. Burdens can also be additive. We propose a heart failure spending function as a conceptual framework for tailored intensification of GDMT that maximizes therapeutic opportunity while limiting adverse events and patient burden. Each patient is conceptualized to have reserve in physiological and psychosocial domains, which can be spent for a future return on investment. Key domains are blood pressure, heart rate, serum creatinine, potassium, and out-of-pocket costs. For each patient, GDMT should be initiated and intensified in a sequence that prioritizes medications with the greatest expected cardiac benefit while drawing on areas where the patient has ample reserves. When reserve is underspent, patients fail to gain the full benefit of GDMT. Conversely, when a reserve is fully spent, addition of new drugs or higher doses that draw upon a domain will lead to patient harm. The benefit of multiple agents drawing upon varied physiological domains should be balanced against cost and complexity. Thresholds for overspending are explored, as are mechanisms for implementing these concepts into routine care, but further health care delivery research is needed to validate and refine clinical use of the spending function. The heart failure spending function also suggests how newer therapies may be considered in terms of relative value, prioritizing agents that draw on different spending domains from existing GDMT.

Key Words: heart failure ■ medications ■ pharmacology ■ polypharmacy ■ quality of health care

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A growing diversity of pharmaceutical agents can improve health outcomes for patients with heart failure with reduced ejection fraction (HFrEF). New evidence from just the last decade supports use of ivabradine,[1] sacubitril/valsartan,[2] dapagliflozin,[3] empagliflozin,[4] vericiguat,[5] and omecamtiv mecarbil.[6] Ideally, all beneficial therapies would be deployed in every eligible patient, as the benefits generally seem to be additive.[7–9] But the burdens of therapy—complexity, overlapping side effects, monitoring, and cost—can also be additive.[7-8] These burdens are further compounded by the high prevalence of multimorbidity and advanced age in patients with HFrEF.[10] Within this context, the real-world use of guideline-directed medical therapies is suboptimal.[11-13] Evidence-based beta-blockers (evBB) are often underdosed; ACE (angiotensin-converting enzyme) inhibitors and angiotensin-II-receptor blockers (ARBs) are infrequently switched to angiotensin receptor with neprilysin inhibitors (ARNi); mineralocorticoid receptor antagonists (MRAs) and hydralazine with isosorbide dinitrate are rarely initiated; SGLT2is (sodium-glucose cotransporter 2 inhibitors) are just beginning to be used.[11] Myriad reasons are cited by clinicians and patients explaining underuse, compounded by therapeutic inertia. We posit a heart failure spending function as a conceptual framework to handle these

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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This manuscript was sent to Kenneth B. Margulies, MD, Guest Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 402.

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Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ARB	angiotensin-II-receptor blocker
ARNi	angiotensin receptor with neprilysin inhibition
eVBB	evidence-based beta-blocker
HFrEF	heart failure with reduced ejection fraction
H-ISDN	hydralazine/isosorbide dinitrate
MRA	mineralocorticoid receptor antagonist
SGLT2i	sodium-glucose cotransporter 2 inhibitor

challenges. The goal is efficient initiation and intensification of heart failure with reduced ejection fraction (HFrEF) medical therapy based on a tailored expected return on investment to achieve favorable health outcomes (Figure). The spending function is an example of personalized medicine that employs the right drug in the right patient at the right dose at the right time. This spending function also suggests how the added value of newer therapies may be considered within the context existing therapeutic spending (Table).

ACCOUNTS, RESERVES, SPENDING, AND RETURN ON INVESTMENT

Patients have physiological reserves in various domains or accounts. These reserves may change over time with exacerbating factors, worsening disease, or, conversely, positive ventricular or vascular remodeling. Therapeutics differentially spend from each of these accounts. Therefore, the tolerability of a therapy for an individual patient depends on the patient's reserve in each account and the amount spent by that therapy.

Overall, the US health system typically underspends on blood pressure, heart rate, serum creatinine, and potassium causing underuse of HFrEF medicines. In the contemporary CHAMP-HF registry, the interquartile range of systolic blood pressure on therapy was 100 to 130 mm Hg and heart rate 66 to 80 beats per minute.[11] Meanwhile, it overspends on cost: branded drugs may be started before similarly beneficial generics,[14] or an echocardiogram repeated rather than dose-intensifying medical therapy. The benefit of multiple agents drawing upon varied physiological domains—similar to the approach of combination chemotherapy that spreads out varied toxicities—should be balanced against cost and complexity associated with polypharmacy. We recommend a more systematic approach that accounts for patient reserves and optimizes return on investment.

HYPOTENSION: BLOOD PRESSURE SPENDING

HFrEF medications often reduce blood pressure: evBB acutely reduce LV contractility, stroke volume, and cardiac output; ACE inhibitor, ARB, and hydralazine cause arteriolar vasodilation and lower systemic vascular resistance; ARNi may exacerbate these hypotensive effects; and diuretics and nitrates can reduce cardiac filling pressures, stroke volume, and cardiac output.[7-8]

Hypotensive effects of HFrEF medications are heterogeneous between classes. The vasodilators ACE inhibitor, ARB/ARNi, and hydralazine with isosorbide dinitrate all significantly reduce blood pressure compared with placebo. In contrast, in RALES,[15] the spironolactone and placebo groups had no difference in blood pressure, and in EMPHASIS[16] the mean difference between eplerenone and placebo was only 2.2 mm Hg at study end. In COMET,[17] at 4 months, the systolic blood pressure decreased 3.8±17.4 mm Hg from baseline with carvedilol and 2.0±17.7 mm Hg with metoprolol. And in DAPA-HF,[3] the mean decrease in systolic blood pressure was −1.5 mm Hg for dapagliflozin versus placebo. Finally, effects evolve over time, as illustrated in V-HeFT I[18] where hydralazine with isosorbide dinitrate group had higher blood pressure than the placebo group by study end.

Not all agents that reduce blood pressure improve HFrEF outcomes. Prazosin has no discernable effect on hospitalization or mortality;[19] diuretics are not beneficial in the absence of congestion; vericiguat primarily reduces hospitalizations but not mortality,[5] and amlodipine does not seem to improve hospitalization or mortality and may increase the risk for pulmonary edema.[20]

Because of a low blood pressure reserve, some patients are more susceptible to hypotension than others. Patients with marginal cardiac output who have compensated through vasoconstriction of less vital vascular beds (eg, skin, muscle, splanchnic) can be worsened by vasodilation of these vascular beds. Patients with marked vasodilation due to cirrhosis, hyperthyroidism, and anemia also tend to have little reserve in the domain of blood pressure. In these cases, hypotension may prevent use of indicated medical therapies. In PARADIGM-HF, the most common reason for sacubitril/valsartan discontinuation was hypotension.[2]

Nonetheless, the optimal treated blood pressure in HFrEF is unknown. Relative risk reductions remain consistent across blood pressure strata in randomized trials of neurohormonal antagonists, and in COPERNICUS[21] the use of evBB in severe disease with relative hypotension conferred consistent relative risk reductions and large absolute benefit. More recently, an analysis of EMPEROR-Reduced trial showed no meaningful interaction of systolic blood pressure and the effects of SGLT2i.[22] However, HF clinical trials tend to enroll younger patients with less comorbidity and eligibility criteria often exclude systolic blood pressure <85 to 90

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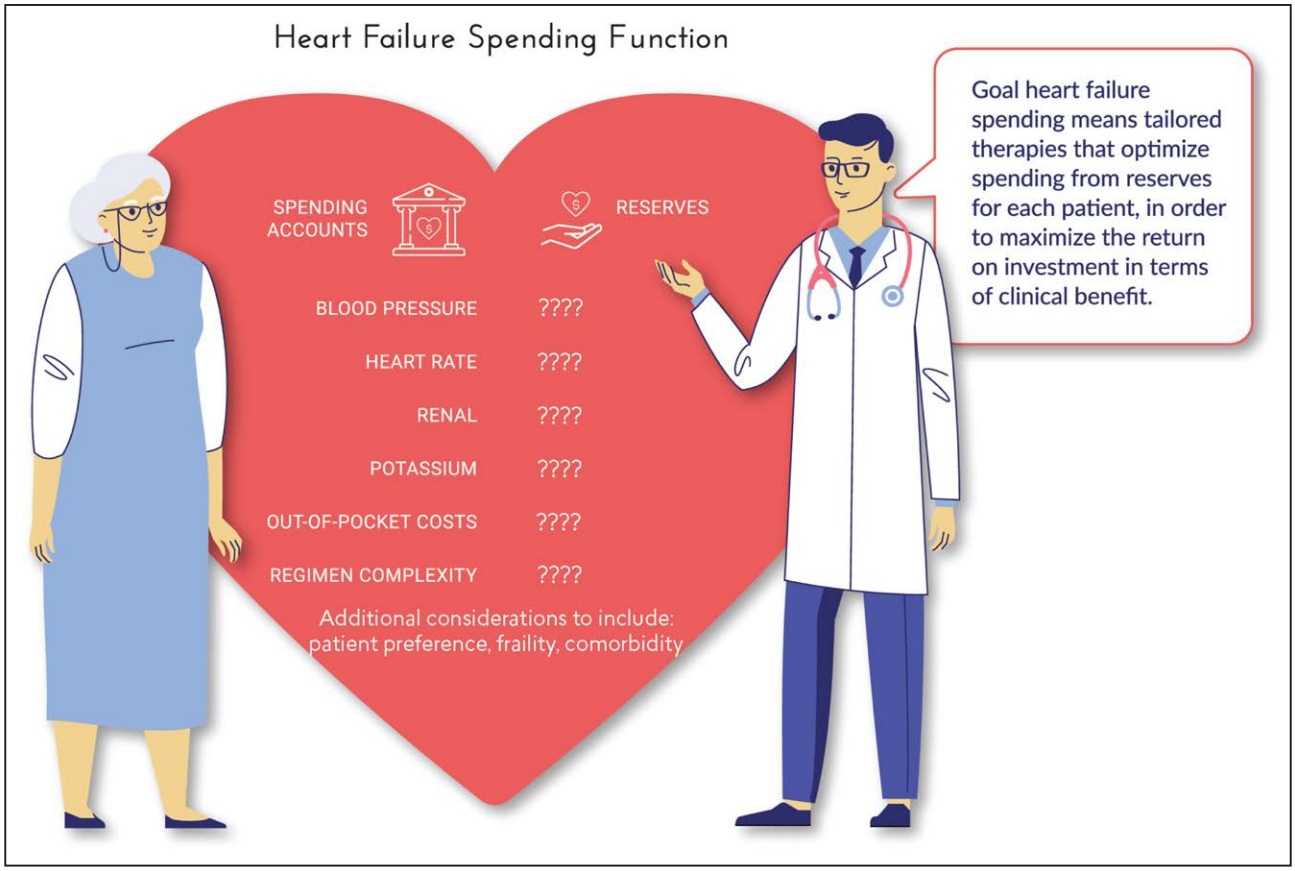

Figure. Conceptualization of the "Heart Failure Spending Function."
Sequencing of guideline-directed medical therapy in a patient with reduced left ventricular ejection fraction should consider how each medication draws upon reserves in various physiological and psychosocial domains within the context of comorbidities, frailty, and patient preferences, to minimize short-term harm and maximize long-term return on investment.

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mm Hg.[7,8] Blood pressure lowering by beneficial neurohormonal antagonists in patients who tolerate them should also be distinguished from spontaneous hypotension or antihypertensive agent intolerance, both of which are poor prognostic markers in HFrEF. The art is differentiating mild, transient hypotension from more severe, persistent hypotension to maximize longer-term treatment benefit while avoiding iatrogenic harm.

We recommend initiation of low doses of evBB, ARNi, and MRA followed by aggressive serial intensification until each medication is at maximal dose or patients are frankly symptomatic from hypotension. When neurohormonal therapies are limited by symptomatic hypotension or systolic blood pressure consistently falls below 90 mm Hg, we suggest treatment by heart failure specialists, with consideration of closer assessment of hemodynamics, and a more gradual step-wise approach to intensification (dose increases ≤50% spaced out longer than every 1–2 weeks).

BRADYCARDIA: HEART RATE SPENDING

Heart rate reducing agents—within normal ranges in sinus rhythm—lead to better HFrEF outcomes. evBB trials show reductions of 10 to 16 beats per minute (bpm) compared with placebo.[21,23] Ivabradine produced an 11 beats per minute decrease compared with placebo at 28 days, which had waned to 7 beats per minute at study end.[1] evBB markedly improve survival and ivabradine reduced hospitalizations.

Within normal ranges reductions in chronotropy often increase stroke volume, such that cardiac output may be relatively stable. However, at heart rates below 50 beats per minute symptomatic impaired perfusion can develop. In COMET[17] after excluding patients with resting untreated heart rates <60 beats per minute, bradycardia was reported in 10% of carvedilol and 9% of metoprolol tartrate-treated patients, leading to serious adverse events in 3% of both groups. In SHIFT,[1] 5% of ivabradine and 1% of placebo-treated patients stopped study drug because of symptomatic bradycardia. Since ivabradine has only been rigorously studied as add-on therapy to evBB, the head-to-head differences between tolerability of ivabradine and evBB are not well defined. Nevertheless, beta-blocker benefits are not solely because of heart rate reduction[23] and seem to be diminished in the presence of atrial fibrillation.[24] Similarly, the impact of evBB when not decreasing heart rate is uncertain: for

Table. Effects by Drug Class: Benefit (Return on Investment) Versus Spending (Limited by Reserves) = Value of Treatment for an Individual Patient

Treatment class*	RRR death	RRR hospitalization	BP†‡	HR†‡	GFR‡	Serum K†‡	$ cost
Loop diuretic	?	?	↓	↔	↓	↓↓	↑
evBB	↑↑↑↑	↑↑↑↑	↓	↓↓↓	↓	↓	↑
RAi							
ACEi	↑↑↑	↑↑↑	↓↓	↔	↓↓	↑↑	↑
ARB	↑↑↑	↑↑↑	↓↓	↔	↓↓	↑↑	↑
ARNi	↑↑↑↑	↑↑↑↑	↓↓↓	↔	↓↓	↑↑	↑↑↑
MRA	↑↑↑↑	↑↑↑↑	↓	↔	↔	↑↑↑	↑
H-ISDN	↑↑↑↑§	↑↑↑↑§	↓↓	↔	↓ or ↔	↔	↑
Ivabradine	↔	↑↑	↔	↓↓	↔	↔	↑↑↑
Digoxin	↔	↑	↔	↓	↔	↔	↑
SGLT2i	↑↑↑↑	↑↑↑↑	↔	↔	↔	↔	↑↑↑
sGC vericiguat	↔	↑↑	↓	↔	↔	↔	↑↑↑↑
Omecamtiv mecarbil‖	??	??	↑	↔	↑?	↔	N/A
K binder	↔	↔	↔	↔	↔	↓↓↓	↑↑↑
CRT	↑↑↑	↑↑↑	↑	↔	↑↑	↔	↑↑↑↑
AF ablation	↑↑	↑↑	↑	↑↓	↔	↔	↑↑↑↑
MitraClip	↑↑¶	↑↑¶	↑	↔	↑	↔	↑↑↑↑

ACEi indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor blocker+neprilysin inhibitor; BP, blood pressure; CRT, cardiac resynchronization therapy; evBB, evidence-based beta-blocker; GFR, glomerular filtration rate; H-ISDN, hydralazine+isosorbide dinitrate; HR, heart rate; K, potassium; MRA, mineralocorticoid receptor antagonist; RAi, renin-angiotensin inhibitor; RRR, relative risk reduction; sGC, soluble guanylate cyclase stimulator; and SGLT2i, sodium-glucose transporter 2 inhibitor.

*Drugs within class are typically similar.

†Effects can be positive (treat tachycardia, hypertension, hypokalemia) but become problematic when reserve is low and further treatment creates extremes.

‡With positive cardiac remodeling, later effects can be opposite of initial effects.

§In patients self-identified as Blacks.

‖Not US Food and Drug Administration approved for heart failure with reduced ejection fraction.

¶Results inconsistent between 2 large randomized trials.

example, when heart rate is controlled by atrial pacing, the spending function is obviated but the efficacy of evBB is indeterminate.

As with blood pressure, the optimal heart rate is uncertain. However, almost all data point to a benefit resting heart rates down to 60 to 70 beats per minute, perhaps even 50 to 60 beats per minute. Observational data are confounded, as tachycardia is associated with more severe disease. In the MESA registry, those with heart rate <55 beats per minute had the best survival.[25] In contrast, in the hospitalized GWTG population, mortality increased below 55 beats per minute (but this represented only 5% of the cohort).[26]

We recommend titrating evBB to guideline-recommended doses, symptomatic tolerance, or minimum heart rate of 50 to 60 beats per minute for patients with HFrEF in sinus rhythm. We caution against rates consistently <50 beats per minute. Beta-blockers should be dose-maximized first before adding ivabradine if an elevated heart rate is still present with sinus rhythm. When there is evidence that evBB are not tolerated for other side effects, ivabradine should be considered in the presence of sinus rhythm. For patients in atrial fibrillation, until more data are available, we recommend evBB use, avoiding ivabradine, and consideration of catheter ablation.[27]

RENAL DYSFUNCTION: KIDNEY SPENDING

The cardiorenal connection is well established but highly complex. Heart failure—through increased renal venous pressure or reduced cardiac output with decreased systemic blood pressure—often decreases renal perfusion, lowers clearance, and worsens intrinsic chronic kidney disease. Many HFrEF drugs also can directly affect renal function through a variety of mechanisms.

Spending in estimated glomerular filtration rate is primarily seen with the renin-angiotensin-aldosterone inhibitors. In ACE inhibitor trials, creatinine initially trended higher compared with placebo. In CHARM Alternative,[28] serum creatinine doubled in 5.5% of the 311 patients with serial measures in the candesartan group, compared with 1.6% of 307 assigned placebo. The addition of neprilysin inhibition does not seem to cause further derangement, as renal function in PARADIGM-HF[2] was not significantly different between ACE inhibitor and ARNi groups.

However, while renal clearance may be acutely reduced by ACE inhibitor, ARB/ARNi, MRA, and SGLT2i, the majority of data show these agents improve renal function over time, even in patients with severe renal disease.

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This can occur through reduced stress on the glomerular apparatus itself or through improved renal perfusion from cardiac remodeling. Generally, a small bump in creatinine from acute hemodynamic effects should not prompt their discontinuation. Therefore, as in other spending domains, reassessment of renal reserve should occur serially over time, with dynamic reconsideration of treatments.

The threshold renal dysfunction for initiation, titration, or avoidance of various medications is complex and controversial. Randomized trial exclusion criteria may be too conservative as they were designed to isolate drug effects under optimal conditions. For example, MRA and SGLT2i (sodium-glucose cotransporter 2 inhibitor) are often not used in patients with estimated glomerular filtration rate <30 mL/min per m^2, but their benefits remained consistent with estimated glomerular filtration rate 20 to 30 mL/minute per m^2 in carefully monitored trials of stage 4 chronic kidney disease.[4] Alternatively, estimated glomerular filtration rate cut offs may be too liberal for older patients and those without the ability to adhere to recommended monitoring.

We recommend ongoing intensification of renin-angiotensin-aldosterone inhibition, and other HFrEF medications, with increases in serum creatinine ≤0.5 mg/dL in patients with GFR >30 mL/minute per 1.73 m^2, with serial laboratory monitoring titrated to risk of renal dysfunction. Increases in serum creatinine >0.5 mg/dL should prompt consideration for removal of other nephrotoxic agents, untreated congestion or overdiuresis, and investigation of renovascular disease. ARNi, MRA, and SLGT2i should all be given additional priority, as tolerated, in patients with chronic kidney disease, given the long-term renal benefits seen with these agents, noting that MRA and SGLT2i are currently contraindicated in patients with GFR <30 mL/minute per 1.73 m^2.

HYPERKALEMIA: SERUM POTASSIUM SPENDING

In patients with HFrEF, perturbations in potassium are common and can prompt arrhythmia. Diabetes frequently overlaps HFrEF, leading to type 4 renal tubular acidosis with reduced potassium clearance. Cardiorenal syndrome tends to cause further reductions in potassium excretion. Conversely, loop diuretics and thiazide-type diuretics used to treat congestion can promote rapid potassium loss. Consequently, monitoring and treating serum potassium is central to HFrEF management.

ACE inhibitor and ARB decrease renal potassium excretion. This is beneficial for patients with hypokalemia and hazardous to those who become hyperkalemic. Fortunately, rates of hyperkalemia in patients with HFrEF initiated on ACE inhibitor/ARB are relatively low. Risks depend on how much the potassium reserve has been affected by existing disease, treatments, and diet. In PARADIGM-HF,[2] during the initial month-long enalapril run-in, serum potassium >5.4 mEq/L prompted removal of 174 of 10 521 patients treated with ACE inhibitor, and another 123 of the remaining 9419 patients then treated with ARNi. In the post-run-in period, serum potassium measurements achieved >5.5 mEq/L in 16.1% of ACE inhibitor and 17.3% of ARNi-treated patients.

MRAs also cause hyperkalemia. In RALES,[15] serious hyperkalemia was 2% for spironolactone and 1% for placebo; in EMPHASIS,[16] hyperkalemia hospitalization was 0.3% for eplerenone and 0.2% for placebo. In the real world, a study looking at rates of hyperkalemia before and after publication of the RALES trial showed an increase in emergent hyperkalemic events in Canada[29]; in Get With The Guidelines, MRA prescription at hospital discharge was associated with significant increase in the risk of readmission with hyperkalemia, predominantly within 30 days after discharge.[30] These concerns may partially explain the low use of MRA in practice. These concerns have also motivated burdensome blood testing algorithms promulgated by guidelines: that is, testing at 3 days, 7 days, 28 days, 3 months, and then every 6 months after initiating or increasing MRA.

Meanwhile, evBB seem to have little effect on potassium handling, and loop and thiazide-type diuretics promote potassium loss. Improved cardiac function and changes in diuretics might change the ability to tolerate potassium sparing agents. Diet and underlying renal function have additional implications for the interaction of HFrEF, drugs, and potassium handling.

The optimal serum potassium is controversial. The serum potassium thresholds guiding prescribing have been relatively consistent in MRA trials: >5.0 mEq/L precludes initiation, >5.5 mEq/L prompts dose reduction, and >6.0 mEq/L triggers discontinuation. In well-monitored settings, the benefits of MRA are consistent across serum potassium levels. While observational data suggest that patients with HFrEF and serum potassium in the normal range do better,[31] potassium handling is affected by cardiac and renal disease severity, potentially confounding such observations.

We recommend greater tolerance of mild hyperkalemia—up to 5.5 mEq/L—in the setting of ACE inhibitor/ARB/ARNi and MRA use, assuming the ability for recommended therapeutic monitoring and consistent dietary potassium intake. For patients in whom hyperkalemia is encountered, nutritional consultation for dietary potassium reduction should be pursued, as well as consideration of potassium binders when cost allows.

COST: OUT-OF-POCKET SPENDING

Underappreciated by the medical community, but prominent for patients, is the issue of financial toxicity. The heart failure spending function is most literally applied to actual spending by patients. The financial burden of treatment to patients is related to health insurance

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coverage, personal income and expenses, and perceived relative value. Unfortunately, in the United States, determining future out-of-pocket costs at the time of prescribing is incredibly challenging. For example, by 2018, all Medicare Part D plans covered ARNi, but copays and accessibility varied markedly across plans, by month, and by patient; annual out-of-pocket costs for this one medication could still be $1685.[32] When incorporated into HFrEF treatment plans that may also include other expensive drugs (eg, ivabradine, SLGT2i, potassium binders), and copays for clinic visits, laboratory testing, and device implantation, costs add up. When considered within the context of common comorbidities such as atrial fibrillation (anticoagulant), coronary disease (lipid and anti-platelet therapy), diabetes (insulin and other newer therapies), and lung disease (inhalers), as well as indirect costs (eg, transportation, lost work), expenditures can become untenable. Therefore, clinicians, pharmacies, insurers, and policy makers must do a better job of making costs transparent and incorporating anticipated expenses into medical decision-making. Patients generally want to discuss cost and efforts are being made to infuse cost into treatment discussions, as exemplified by one decision aid: https://www.cardiosmart.org/docs/default-source/assets/decision-aid/heart-failure-drug-options.pdf?sfvrsn=aaff9c98_1.33

We recommend that clinicians actively consider out-of-pocket costs, including them in conversations with patients; that health systems work with payers to make out-of-pocket costs transparent and immediate to real-time care decisions; and that researchers continue to find ways to best communicate costs within the context of therapeutic benefits and overall value.

OTHER COSTS: UNIQUE SPENDING

The domains above are neither clean nor complete. For instance, SGLT2i can cause genitourinary infections, spironolactone may cause gynecomastia, and beta-blockers may cause impotence. Comorbidities can add further complexity. However, we feel those captured here are most helpful to keep front of mind.

POLYPHARMACY: COMPLEXITY SPENDING

Patients with HFrEF take an average of >10 medications.[34] This polypharmacy is because of multiple factors: the expansion of HFrEF-specific therapies, high multimorbidity, and the propensity of HFrEF to affect older populations with frailty and dementia, those with unfavorable social determinants of health, and those with lower health literacy. While the spending function framework may argue at times to use multiple medications at lower doses to spread out toxicity, that approach can conversely increase patient burden in terms of required education, pill burden, and cost. For a stable patient with HFrEF who has heretofore been managed with furosemide, metoprolol succinate, lisinopril, and spironolactone every morning, there are multiple opportunities to improve HFrEF therapy; but they generally increase the number, frequency, monitoring, or cost of treatment. A patient-centered approach that tailors medication decisions to where patients have the most reserve is best.

We recommend that clinicians consider total number of prescriptions, times per day to take medications, and prescribing changes, with weight given to approaches that reduce therapeutic complexity. For example, starting with ARNi rather than switching over from ACE inhibitor with a 36-hour delay is simpler and better for patients hospitalized with new HFrEF.[35] In patients with diabetes and HFrEF, adding SGLT2i may hit two birds with one stone.

THERAPIES THAT INCREASE SPENDING RESERVES

Achieving optimal volume status is central to controlling HFrEF symptoms and optimizing reserve in many domains. Patients who are congested are less likely to tolerate the hemodynamic effects of evBB and the renal effects of ACE inhibitor/ARB/ARNi. Conversely, overdiuresis and dehydration lead to impaired cardiac function, hypotension, and renal dysfunction.[36] Therefore, loop diuretic titration to achieve optimal filling pressures can increase reserve in many domains, enabling spending on therapies with long-term benefit. Various analyses of CardioMEMS data suggest that one of the potential mechanisms for benefit is through increased initiation and intensification of neurohormonal antagonist therapies in addition to meticulous diuretic management.[37] Use of loop diuretics to treat congestion also lower potassium, and thus addition of MRA at the time of loop diuretic initiation may represent a balanced strategy to preserve potassium homeostasis while accelerating neurohormonal antagonist intensification. Inpatient MRA initiation has been illustrated as safe in ATHENA-HF[38]; yet, the majority of Americans hospitalized with worsening HFrEF are discharged without MRA.[11]

Some therapies are now designed to loan spending power by offsetting side effects through increased reserve in a specific domain. The most obvious examples are the newer potassium-binders—patiromer and sodium zirconium cryosilicate—that can hold potassium in the normal range, and potentially allow for continuation of ACE inhibitor/ARB/ARNi and MRA despite the development of hyperkalemia.[39] However, they add therapeutic complexity, add cost, and require adherence for safety of ongoing medication use; they theoretically exacerbate hypokalemia and hypomagnesemia; zirconium contains

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sodium; and they have not been studied in cardiovascular outcomes trials. To this last point, therapies that improve a domain must be assessed for adverse effects and overall benefit. For example, the technique of using midodrine or fludrocortisone to increase blood pressure in heart failure patients is associated with worse long-term outcomes.[40]

Therapies that improve cardiac function are likely to improve reserve across many spending domains. Cardiac resynchronization therapy can improve contractile efficiency, consequentially improving reserve in multiple areas related to cardiac power. For patients with left bundle branch block who continue to bump up against hypotension and renal dysfunction, cardiac resynchronization therapy responders are shown to have increased tolerability of guideline-directed medical therapies after implant, occasionally rescuing patients with end-stage disease on a calcitrope infusion.[41]

Rescuing patients in shock with a positive inotrope leading to eventual downstream transition to guideline-directed medical therapies is well described. Simultaneous use of calcitropes with evBB is more controversial. The phosphodiesterase-3 inhibitor milrinone produces favorable hemodynamic effects in patients treated with the evBB, whereas the beta-agonist dobutamine does not.[42] Long-term use of calcitropes generally worsens clinical outcomes over time.[43] Omecamtiv mecarbil, a novel myotrope, increases cardiac performance through prolongation of systolic contraction, spending in the unique domain of diastolic time. In the GALACTIC-HF trial, hospitalization was decreased with no change in survival.[6]

Mechanical circulatory support directly improves hemodynamics—blood flow, blood pressure, and renal perfusion—and thus may allow for improved neurohormonal antagonist use in advanced disease with reversible cardiac dysfunction. However, a decade of work into cardiac recovery among patients with durable left ventricular assist devices shows this approach to be limited.[44]

We recommend a creative and patient-centered approach to therapeutic combinations, working around depleted spending domains. Future research should prioritize novel treatments with unique mechanisms that spend in different domains than existing therapies.

SPECIAL POPULATIONS: SPENDING IN PATIENTS WITH ADVANCED AGE AND MULTIMORBIDITY

Heart failure is largely a disease of older people with multiple chronic conditions. The average age of an American discharged from the hospital following a heart failure exacerbation now exceeds 78 years old. The average patient with HFrEF has 4.4 comorbidities.[10] Such older, frail populations have less reserve in various domains. Yet, many studies show preserved relative risk reductions in this population,[45] such that the absolute benefits of targeted therapies in this high-risk population may be robust.

Unfortunately, most of the high-quality data that we have about therapeutic efficacy, and side effects, come from randomized trials that enrolled a younger, healthier, male population. Phase 4 postapproval studies and observational registries provide important data on safety events in a much broader population and may help suggest which patients lack reserve in certain areas and what therapy combinations are best tolerated by various types of patients.

We recommend potentially slower intensification of therapies and more careful monitoring for side effects in older patients and those with multiple comorbidities. This approach should not exclude therapy consideration in such populations with reasonable expectations of future function and survival; alternatively, these high-risk populations may see greater return on investment, as spending domains allow.

THE SEQUENCING CONUNDRUM AND HOW A SPENDING FRAMEWORK HELPS US SOLVE IT

The sequencing of HFrEF medications has become increasingly complicated and central to HFrEF management. Clinicians should work progressively from the therapy with the highest value to the lowest, determined for each patient at each point in time. evBB consistently show large reductions in long-term morbidity and mortality, and they are inexpensive to patients and society; spironolactone is similar and can be combined with loop diuretics at the time of initial presentation.[38] But for patients with bradycardia or severe decompensation, hyperkalemia or inability to do laboratory testing in follow-up, or a host of other individual factors, the use of evBB or MRA may have excess short-term cost. Thinking about each patient from the perspective of where they have the greatest reserves—and, conversely, where they currently have no reserve—should help direct sequencing of treatment intensification. This determination of personalized value for each therapy requires integration of the range of expected health outcomes—anticipated absolute survival and quality of benefits minus risks, side effects, and burdens. Disease severity, actual side effects, and out-of-pocket costs often change over time, so this integrative approach also requires frequent reassessment.

Future research may provide greater insights into personalizing therapies for individual patients. The BIOSTAT-CHF group analyzed 92 cardiovascular biomarkers and found 6 profiles with different clinical characteristics and outcomes, as well as potentially different responses to uptitration of HFrEF therapies.[46] Furthermore, the current movement

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toward greater shared decision-making fits nicely with the spending function.[47] Patient-reported symptoms critically inform assessment of many reserves. And patient values, goals, and preferences for care help determine the individual value of each therapy for a given patient.[48]

CONCLUSIONS

The heart failure spending function framework can help promote tailored intensification of HFrEF medical therapy with the least adverse events and patient burden. This spending function suggests how newer therapies may be considered and prioritized in terms of added total value, particularly when they do not draw on domains spent by other agents. The goal is a greater return on investment by proactively employing tolerable guideline-directed medical therapies early and often to maximize long-term gains in health outcomes. Further health care delivery research is needed to validate and refine more detailed algorithms and recommended spending thresholds, but the concepts captured in the heart failure spending function can be used today by clinicians to promote higher-value care.

ARTICLE INFORMATION

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Acknowledgments

The authors thank Robbin Moisa, MD, for her assistance in coordinating the production of this article.

Disclosures

Dr Allen reports grant funding from the American Heart Association, the National Institutes of Health, and the Patient-Centered Outcomes Research Institute and consulting fees from Abbott, ACI Clinical, Amgen, Boston Scientific, Cytokinetics, and Novartis. Drs Teerlink, Gottlieb, Ahmad, Lam, and Psotka report consulting fees from Cytokinetics.

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