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COMORBIDITIES (J. TROMP, SECTION EDITOR)

Polypharmacy in Older Heart Failure Patients: a Multidisciplinary Approach

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Abstract

Purpose of Review We provide a review of considerations when applying principles of optimal pharmacotherapy to older adults with heart failure (HF), an analysis on the pivotal clinical trials focusing on applicability to older adults, and multidisciplinary strategies to optimize the health of HF patients with polypharmacy.

Recent Findings Polypharmacy is very common among patients with HF, due to medications for both HF and non-HF comorbidities. Definitions of polypharmacy were not developed specifically for older adults with HF and may need to be modified in order to meaningfully describe medication burden and promote appropriate medical therapy. This is because clinical practice guidelines for multi-drug HF regimens have unique considerations, given that they improve outcomes and symptoms of HF.

Summary Adults older than 65 years are well represented in contemporary clinical trials for HF with preserved ejection fraction (HFpEF) and guideline directed medical therapy (GDMT) for HF with reduced ejection fraction (HFrEF). While these trials did not have significant heterogeneity in safety or efficacy across a broad age spectrum, some may have limited representation of adults ≥ 80 years old, the sickest older adults, or those with decreased functional status. There is also a lack of data on the safety and efficacy of deprescribing HF medications, and deprescription in otherwise stable patients may lead to clinical destabilization or disease progression. There is therefore innate tension between the well-studied benefits of optimized HF therapy for older adults that must be weighed against the risks of polypharmacy and many unknowns that still exist. Given the strong evidence that optimized HF therapies confer symptomatic and mortality benefits for older adults, it is clear that polypharmacy in this context can be appropriate. A shift in paradigm is therefore needed when evaluating polypharmacy in patients with HF. Instead of assuming all polypharmacy is "good" or "bad," we propose a concerted move, using a multidisciplinary approach, to focus on the "appropriateness" of specific medications, in order to optimize HF medical therapy. Clinicians of all specialties caring for complex older adults with HF must consider goals of care, functional status, and new evidence-based therapies, in order to optimize this polypharmacy for older adults.

Keywords Polypharmacy · Heart failure · Older adults · Multi-disciplinary · Guideline-directed medical therapy

This article is part of the Topical Collection on *Comorbidities*

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Introduction

Heart failure (HF) disproportionately affects older adults (adults ≥ 65 years old) and has been referred to as a sixth geriatric syndrome [1]. The mean age at onset of HF in the USA is ≥ 70 years, and the prevalence of HF increases with age. Data from the National Health and Nutrition Examination Survey (NHANES) shows the prevalence of HF in those 40–59 years old is 1.2% for women and 1.5% for men, rising to 4.8% and 6.6% for those 60–79 years old, and 13.5% and 10.6% for those ≥ 80 years old [2]. HF is the leading cause of hospitalization for adults older than 65 years [3], and more than 70% of hospitalizations for HF are for patients ≥ 65 years old [1, 4]. Among older adults hospitalized for HF, 25% are readmitted within 1 month, and 70% are readmitted within 1 year [5, 6].

There are unique considerations for HF in older adults; clinical practice guidelines may not adequately address the needs of these complex patients who often experience geriatric syndromes [7, 8]. Geriatric syndromes (such as incontinence, falls, functional decline, and cognitive impairment) are associated with worse HF prognoses [9], and the presentation and management of HF in older adults lies at the intersection of multiple geriatric considerations including complex medical disease, physical and cognitive function, environmental factors, and physiologic processes that impact health beyond left ventricular ejection fraction [9].

One of these complex considerations is polypharmacy. Polypharmacy is generally described as taking ≥ 5 medications and is considered both a cause and consequence of geriatric syndromes. A growing global issue, polypharmacy is driven by the successful development of treatments for multiple chronic conditions, the rising prevalence of multimorbidity, and numerous evidence-based guidelines for medical management [10, 11]. Most older adults with HF experience polypharmacy, and polypharmacy increases with age [12].

While there is ample literature on polypharmacy in older adults and strategies for safe deprescription [13], it is unclear how to apply traditional principles of pharmacotherapy (such as definitions, appropriateness of deprescription, and methods for optimization) to older adults with HF, in whom polypharmacy is inevitable and often unavoidable.

We provide a review of considerations when applying principles of optimal pharmacotherapy to older adults with HF, an analysis on the pivotal clinical trials focusing on applicability to older adults, and multi-disciplinary strategies to optimize the health of HF patients with polypharmacy.

Defining Polypharmacy in Older Adults With HF

While there is no clear, universal definition for polypharmacy [10], an individual concurrently taking ≥ 5 medications is considered to have polypharmacy [14]. This includes prescribed medications, over-the-counter medications, and dietary supplements that are regularly used [11]. Table 1 summarizes key studies with data on polypharmacy and HF.

It is unclear if the typical definition of polypharmacy discussed above has meaning within the context of HF, given how ubiquitous polypharmacy is in this population.

Table 1 Burden of polypharmacy among older adults

	2020, Wu et al.[15]	2020, Unlu et al.[16]	2021, Navid et al.[17]
Population characteristics	HFpEF, retrospective analysis of TOPCAT	Observational study of 65 + hospitalized for HF	HFpEF, Retrospective cohort at program providing care to older adults with HfpEF 07/2018–12/2019
Sample size	1761	550	134
Average age	72 (64–79)	76 (72–82)	75 (69–82)
Prevalence of polypharmacy	38%	84% at admission 95% at discharge	94%
Prevalence of hyperpolypharmacy	36%	42% at admission 55% at discharge	56%
Prevalence of super hyperpolypharmacy	19%	Not studied	Not studied
CV and non-CV medications most commonly implicated	CV: statin, ACEi, ASA, BB, diuretic Non-CV > CV	CV: ASA, BB, Statin, loop diuretic, ACEi Non-CV: PPI electrolyte supplements, MVI, thyroid hormone, SSRI adrenergic bronchodilator Non-CV > CV Non-HF > HF	N/A

For instance, in a 2020 observational study of older adults hospitalized for HF, 84% at admission were prescribed ≥ 5 medications and 42% were prescribed ≥ 10 medications (increased to 95% and 55%, respectively, at the time of discharge) [16]. There is therefore ongoing discussion in the geriatrics and cardiology literature about whether the conventional numeric and binary definition of polypharmacy can be generalized to older adults with HF [18, 19]. These discussions include calls to modify the definition of polypharmacy to one that has greater clinical utility in describing medication burden.

Given that up to 50% of patients with HF are prescribed ≥ 10 medications, some have suggested a threshold of 10 is more appropriate for defining clinically significant polypharmacy in these patients [16]. While a change in the binary definition of polypharmacy may be useful, another categorization system is as follows: those with 5–9 medications ("polypharmacy"), 10–14 medications ("hyper-polypharmacy"), and ≥ 15 medications ("super-polypharmacy") [15].

However, these definitions still focus on the number of medications, rather than the appropriateness of specific medications [20]. In other words, while referred to as a "necessary evil" [21], polypharmacy as a label (even with a modified definition for specific chronic diseases) does not tell us if the numerous medications a patient takes are "appropriate" or "inappropriate" [22]. Figure 1 lists factors that help determine the appropriateness of a certain medication.

Causes of Polypharmacy in Those With HF

a) Medical management of concomitant medical conditions: The number of chronic comorbid health conditions is an independent predictor of polypharmacy [16, 19]; 90% of patients with HF have ≥ 3 comorbid conditions and 50% have ≥ 5 [23]. Interestingly, the majority of medications prescribed for those with HF may not be for cardiovascular (CV) indications [16]. When trends in medication prescription during hospitalization were studied, non-CV medications present on admission and discharge increased more than HF-related or CV-related medicines [16]. Data from NHANES also shows that the rise in polypharmacy over time for patients with HF is mostly driven by increases in management of HF-associated comorbidities such as hyperlipidemia, diabetes, obesity, kidney disease, thyroid disease, and osteoporosis [7]. The prevalence of polypharmacy in older adults with HF is therefore rooted in multi-morbidity and the concurrent medical management of non-HF conditions [24].

b) Guideline recommended medical management of HF: Of note, the estimates above were from studies conducted prior to the availability of angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose cotransporter-2 inhibitors (SGLT2i). All patients with HFrEF able to tolerate guideline-directed medical therapy (GDMT) will now meet criteria for four or more medications—beta-blocker (BB), mineralocorticoid receptor antagonist (MRA), ARNI, and SGLT2i [12]. With the addition of each new and effective pharmacotherapy for HF, and evolving guidelines recommending multi-drug treatment regimens for HF, there is concern that guideline-based treatment for HF will further increase polypharmacy.

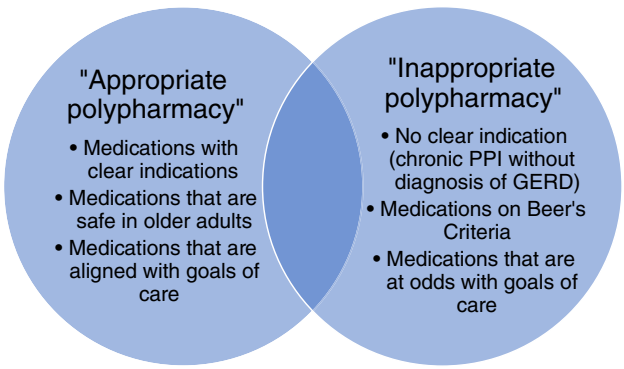

Fig. 1 Important considerations when assessing the appropriateness of individual medications and multi-drug regimens. This proposed framework helps change the narrative of polypharmacy to a nuanced analysis with the goal of optimizing medication regimens for an individual

Risks of Polypharmacy

Risks of polypharmacy include adverse drug events [25–27], increased hospitalizations [25, 28, 29], poor patient experience [30–32], financial burden [33], and prescribing cascades [34]. Each are reviewed below.

Adverse Drug Events

Adverse drug events are linked to altered pharmacokinetics and pharmacodynamics with aging [35, 36]. Adverse drug events are a large cause of emergency room visits in older adults, and CV medications such as metoprolol and lisinopril are among the 15 most frequent drugs implicated in emergency room visits [37]. Fifteen percent of older adults are at risk for a drug-drug interaction (DDI) [11]. In addition, many medications are known to either cause or exacerbate HF [38]. Adverse effects of medications specific to HF management are included in Table 2.

Table 2 Representation of HF clinical trials for older adults with polypharmacy

	Clinical trial	Average age, IQR	Percent of study population age > 65, PPR (assuming prevalence of HF is < 10%) [39]	Percent of study population age > 75, PPR (assuming prevalence of HF is < 10%) [39]	Percent of study population age > 80, PPR (assuming prevalence of HF is < 25%) [40]	Efficacy outcomes (mortality, hospitalization, EF, etc.)	Adverse effects/safety profile
ARNI	*Paradigm-HF (2014) [41]	63.8 ± 11.5	> 25%, > 2.5	~ 25%, 2.5	< 25%	Lower CV death and HF hospitalization	Cough, hyper K, renal dysfunction, hypotension
	Pioneer-HF (2019) [42]	61 ± 10	> 25%, > 2.5	< 25%	< 25%	Lower BNP	
	Paragon-HF (2019) [43]	72.7 ± 8.3	> 50%, > 5	> 25%, > 2.5	~ 25%, 1	HF hospitalization & CV death	
SGLT2i	DAPA-HF (2019) [44]	66.2 ± 11	> 50%, > 5	> 25%, > 2.5	< 25%	Worse HF (hospitalization/urgent visit with IV therapy)	Hypovolemia, renal dysfunction, ketoacidosis, UTI (severe seen in post marketing), hypoglycemia
	Emperor-Reduced (2020) [45]	67.2 ± 10.8	> 50%, > 5	> 25%, > 2.5	< 25%	CV death and hospitalization	
	Emperor-Preserved (2021) [46]	71.8 ± 9.3	> 50%, > 5	> 25%, > 2.5	~ 25%, 1	CV death and hospitalization	
ACE	CONSENSUS (1987) [47]	70	> 50%, > 5	Unknown	Unknown	Mortality	Hypotension
	SOLVD (1991)[48]	61	Unknown	Unknown	Unknown	Mortality, CV death, HF hospitalization, hospitalization	Hyperkalemia, elevated Cr
ARB	CHARM Alternative (2003) [49]	66.8	> 50%, > 5	Unknown	Unknown	CV death, HF hospitalization	Cough, hypotension, renal dysfunction, hyperkalemia, angioedema
BB	CIBIS-II (1999) [50]	61	Unknown	Unknown	Unknown	Mortality	Stroke, bradycardia
	MERIT-HF (1999) [51]	64.4	Unknown	Unknown	Unknown	Mortality, hospitalization, CV death	
MRA	EMPHASIS-HF (2011) [52]	68.7 ± 7	> 50%, > 5	25%, 2.5	< 25%	CV death, HF hospitalization	Hyperkalemia
Ivabradine	*SHIFT (2010)[53]	60	Unknown	Unknown	Unknown	HF mortality, hospitalization, death, CV mortality, NYHA Class, HR reduction	Symptomatic bradycardia, visual side effects

* New Drug Application efficacy trials approved for marketing by FDA

Hospitalizations

In a retrospective analysis of the "Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist" (TOPCAT) trial, high medication burden was associated with increased hospitalization [15].

Patient Experience

polypharmacy is associated with decreased quality of life and more disability [30–32]. High medication burden can lead to non-adherence or inaccurate medication administration. Many older adults want to decrease their medication burden and discuss decreasing the number of medications they take with their clinician [54].

Financial Considerations

Financial burden is increasingly a concern with expensive ARNI, SGLT2i, and medications for comorbidities [33].

Prescribing Cascade

This includes a prescribing "cycle" of medications to counter adverse effects of previously prescribed medications [34] (e.g., prescribing potassium supplementation to treat hypokalemia caused by loop diuretics).

Are the Clinical Trials for HF Medical Management Generalizable to Older Adults?

It is important to understand the generalizability of the HF clinal trials to older adults, since this will contextualize medication risks and benefits. While many clinical drug trials do not include older adults, recent HF trials have been more representative of adults 65 years or older. Table 2 shows the prevalence of HF amongst older adults stratified by age. Participation to prevalence ratios (PPR) were used to determine representativeness of the different age groups (using conservative measurements to overestimate the prevalence of HF in each group), in which a PPR < 0.8 indicates underrepresentation, 0.8–1.2 indicates adequate representation, and > 1.2 indicates overrepresentation [39].

The three most recent HFpEF trials all had mean population ages 72–73 years, with large proportions of those ≥ 80 years old. Table 2 shows that all subgroups of age were represented well in the HFpEF trials for ARNI and SGLT2i. While most trials for ARNI and SLGT2i in those with HFrEF were representative of those ≥ 65 years old and ≥ 75 years old, it is unclear if those ≥ 80 years old were adequately represented in these trials. This is supported by preliminary US Food and Drug Administration (FDA) data for new drug approvals that compared the prevalence of HF in community dwelling adults ≥ 80 to the representation of these patients in clinical trials (Fig. 2) [40]. These results support the finding that there is adequate clinical trial representation of adults with HF age 40–79, but a scarcity of data for those ≥ 80 years (despite high prevalence of disease in this population).

Within the clinical trials for HF, efficacy of the drugs was maintained across age bands. Safety profiles were similar across age groups, with evidence that sacubitril-valsartan had a higher risk of hypotension in older patients [55]. However, post-marketing data has unveiled risks to older adults not seen in the original clinical trials. In 2015, the FDA revised labels for all SGLT2i adding a warning for severe UTIs based on post-marketing adverse event reports of sepsis and pyelonephritis. While SGLT2i mostly cause mild to moderate urinary tract infections (UTI) [56, 57],

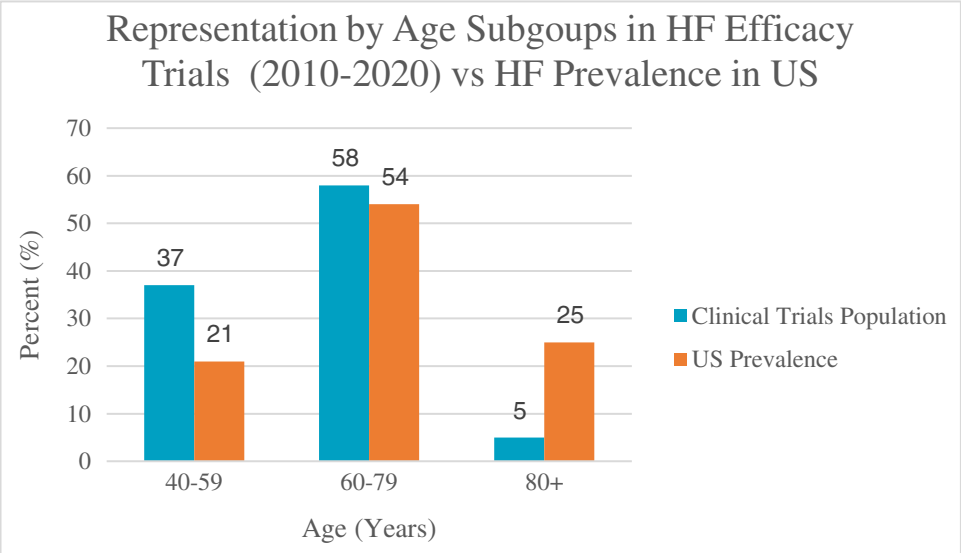

Fig. 2 Preliminary data from the FDA showing there is adequate clinical trial representation of adults with HF age 40–79 from 2010 to 2020 [40]. There is a relative scarcity of data for those ≥ 80 years old, despite high prevalence of disease in this population

such side effects significantly impact the quality of life for older adults who are at higher risk for these infections. Post-marketing data also analyzed the effectiveness and safety of sacubitril-valsartan vs angiotensin receptor blockers (ARB) [58, 59]. In a Medicare population, sacubitril-valsartan had more adverse effects in both frail and non-frail older patients with HFrEF, including hypotension and AKI, compared to that seen in clinical trials. The mean age of this population was 76 years vs 64 years in the pivotal ARNI trial, "Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure" (PARADIGM-HF), and these patients had a higher prevalence of diabetes, atrial fibrillation, and history of stroke than the population studied in the clinical trial. While the authors acknowledged unmeasured confounding, these results suggest nuanced considerations when prescribing GDMT in those who may be older, sicker, and frailer than those included in clinical trials, despite the overall inclusion of "older adults" in these studies. In summary, although the HF clinical trials included many older adults, additional work is needed to increase representation of older adults in HF clinical trials adults beyond chronologic age [60] and study outcomes such as functional status, frailty, geriatric syndromes, and time to benefit.

Argument for "Appropriate Polypharmacy" in Older Adults With HFrEF

While polypharmacy is often discussed as a "problem" to be fixed with deprescribing, this paradigm is not always appropriate for those with HF [19]. Even outside the context of HF, there is acknowledgment about the necessity of prescribing 5 or more medications, despite the known risks, when the prescribed medications have appropriate indications [10]. An even stronger argument can be made that within the context of HF, the known benefits of optimized medical management outweigh the risks of polypharmacy for older adults [61].

For example, a meta-analysis of combination use of ARNI, BB, MRA, and SGLT2i for HFrEF estimated a reduction of all-cause death compared to regimens only including a few of these medications [62]. The analysis showed that the expected life-years gained for a 70-year-old on that multidrug regimen was 5 years compared with no treatment. A cross-trial analysis of pivotal HFrEF drug trials comparing 2 agent "conventional treatment" (ACEi/ARB with BB) with "comprehensive therapy" of 4 agents (ARNI, BB, MRA, SGLT2i) showed decreased CV mortality or HF-related hospitalization by 62% [63]. These effects were largest in younger patients, but also significant in older patients. This multi-drug regimen was estimated to provide an 80-year-old with 2.7 additional years free from CV death or first hospital admission for HF and 1.4 years of survival compared to conventional treatment.

In addition to increasing survival, there is strong data from clinical trials that GDMT confers symptomatic benefit (Table 2) that may be important to older adults as they age (unlike aspirin or statins that prolong life or decrease hospitalizations without symptomatic benefit). There is also a lack of data on the safety of not prescribing GDMT for those with HF who can tolerate it, and there are few outcome studies of attempts to deprescribe GDMT. The "Withdrawal of Pharmacologic Treatment for Heart Failure in Patients with Recovered Cardiomyopathy" (TRED-HF) trial studied outcomes for patients with previously dilated cardiomyopathy with recovered left ventricular ejection fraction and found that 44% of patients assigned to HF treatment withdrawal had relapse of disease (compared to 11% in those assigned to continued treatment) [64]. This relapse of disease often led to re-prescription of HF medications.

Patients are also likely to have adverse effects after discontinuing HF medications. Discontinuing HF medications such as beta blockers, diuretics, and antihypertensives also has a risk of adverse withdrawal effects include hemodynamic changes, symptomatic hypervolemia, and hypertension [13].

Polypharmacy is a physician-reported barrier to the appropriate initiation of GDMT, and eligible older adults who may benefit from the mortality or symptomatic benefits of GDMT are disproportionately not given GDMT by their clinicians [65]. There is the concern that clinicians trying to avoid polypharmacy (with a "standard" definition as 5 medications) may inappropriately avoid prescribing optimized medical therapy when it is appropriate and indicated [22], and this may be harmful for patients with HF.

Special Considerations for HFpEF

Among older adults with HF, HFpEF is more common than HFrEF [66]. Despite the lack of strong indication for GDMT in these patients, polypharmacy is as common in HFpEF as in HFrEF. This is possibly because of the high burden of medicines prescribed for non-HF comorbidities [16]. In a study of 134 consecutive patients with HFpEF (median age of 75 years old), almost 94% had ≥ 5 medications, and 56% had 10–14 medications [17]. Adults ≥ 80 years old may also be better represented in the HFpEF trials than HFrEF trials (as discussed above and described in Table 2). Given that many medications for HFpEF will increasingly be targeting QOL alone and not mortality and hospitalization, their impact in older adults will need to be more carefully studied.

Strategies to Optimize Polypharmacy in Older Adults with HF

Non-geriatrician clinicians, who may not have expertise in geriatric pharmacotherapy, will increasingly be caring for older adults with HF. Collaborative frameworks, tools, and systems innovations will be essential for these providers to manage and optimizing polypharmacy (Fig. 3).

Multidisciplinary Clinics

Using warfarin clinics, cardiac rehabilitation, and the Program of All-Inclusive Care for the Elderly (PACE) as models for interdisciplinary cardiac care [17, 20, 22], management of complex older adults with HF and multiple prescriptions might be best centered around a multi-disciplinary team including geriatricians, cardiologists, pharmacists, nurses, and caregivers [22]. Such teams may be useful in not only optimizing holistic care for complex patients with multiple comorbidities and HF, but also in providing successful and safe strategies for prescription and deprescription [67]. Careful care coordination and communication are essential, especially in a setting where patients will benefit from different team members providing diverse experiences and expertise [19]. For instance, there is data that pharmacist-run HFrEF clinics improve patient care and lead to earlier initiation of GDMT, more frequent follow-up, and better patient education [68]. This is especially important in settings where patients may not have access to heart failure specialists or geriatricians, but who will still interface with pharmacists [69].

Domain Management Approach

Another holistic strategy for optimizing HF and polypharmacy is that of the Domain Management Approach [9, 18]. This includes optimizing individual medications as described below, and also optimizing the patient's physical function, emotional and mental well-being, and social environment. For instance, collaborating with caregivers to evaluate and optimize home safety can help mitigate the fall risk associated with polypharmacy and orthostatic hypotension that may result from HF medical treatment.

Fig. 3 Ecosystem of medical and social considerations and resources that need to be coordinated to provide healthcare for older adults with HF and optimize polypharmacy. A multidisciplinary clinic can serve as a medical home for complex patients and their caregivers, navigating these various resources and recommendations

Initiating Medications

Evidence-based guidelines need to be balanced with minimizing unnecessary medications, avoiding prescribing cascades, and minimizing adverse symptoms [19]. For instance, initiating treatment with MRA, when indicated, may limit the need for potassium supplementation in HF care [16]. When prescribing new medications, clinicians should aim to prescribe few new medications at the same time and begin each drug at a low dose, gradually increasing dosing as appropriate [70]. Alternately, one might consider time-limited trials of new medications with unclear benefits. Resources such as monthly punch cards of pre-organized pills, patient education, and mail-in pharmacies might decrease the risk of accidental overdose or non-adherence. There may also be a role for telemedicine to remotely monitor patients after initiation of new medications, although this can be challenging for older adults with limited internet literacy or sensory impairments.

Reviewing Existing Medications

Clinicians must closely monitor and address geriatric syndromes that are side effects of multiple medications used to manage HF (falls [71], cognitive impairment [72–74], ototoxicity/hearing loss, bleeding from falls, orthostasis, nocturia, lower urinary tract symptoms) using the domain approach above. Reducing cognitive burden and risks of managing multiple medications is also recommended (for instance, optimize timing of medications so that patients can take pills at the same time every day, retime diuretics and anti-hypertensives to avoid nocturia or nighttime orthostatic hypotension that can lead to falls). Clinicians should also review how patients take their medications at each encounter.

Appropriate Deprescribing

As discussed above, there is a strong argument to use caution before deprescribing indicated medications for HF management. There may be benefit to the thoughtful consideration of deprescribing other CV and non-CV medications, including harmful, overlapping, interacting, or neutral therapies [75–77]. However, it is unclear if deprescribing practices are effective at decreasing the number of medications a patient takes or improving outcomes. There is a lack of data on how to safely implement such strategies, few proposed frameworks for deprescription within cardiology context [54], and a lack of data on outcomes and risks for deprescribing HF medications. Recent data suggests that deprescribing may barely lower medication usage [78], and it might not lead to a reduction in adverse drug events [79]. Large trials studying deprescription for older adults have largely focused on sedative-hypnotic medications for older adults (especially those with cognitive impairment), and the generalizability of such trials to HF is limited [80]. There is a National Action Plan targeting deprescription of specific drugs, but this does not include cardiac medications.

That being said, different physicians caring for older adults with CV disease do consider deprescribing, but often for different reasons [81]. A study on deprescribing practices shows that 80% of general internists, geriatricians, and cardiologists reported recently considering deprescribing CV medications (most often due to adverse side effects) [81]. In this same study however, there were variations between specialty regarding the impetus for deprescribing. Geriatricians were most likely and cardiologists least likely to consider deprescribing CV medications for patients with limited life expectancy (recurrent metastatic cancer, Alzheimer's disease, significant functional impairment). Barriers to deprescribing reported in this study included patient preference and clinician concerns about changing another clinician's plans. More cardiologists reported not deprescribing due to insufficient evidence of deprescribing benefits than geriatricians or internal medicine physicians. Interestingly, $< 10\%$ of providers noted hyperpolypharmacy as the indication for deprescribing. Overall, polypharmacy on its own did not seem to play as large a role as other related indications for deprescription, such as adverse side effects.

Decision Aids

The availability of explicit tools to aid decision-making for patients with HF might simplify the process of optimizing the health of those with polypharmacy [82]. Multiple online tools are available to aid in decision-making, monitoring, and discontinuation [83–85]. These include Medstopper.com, deprescribing.com, Eprognosis, Medication Appropriateness Index, STOPP/START [86], the Geriatrics Deprescribing Protocol (Fig. 4, modified to include the role of appropriately re-prescribing medications) [87], and the FORTA list [82]. Given evidence discussed above that polypharmacy may increase during hospitalizations of those with HF, electronic inpatient-centered clinical decision-making tools as studied in the MedSafer study may also be beneficial [79]. Review of the literature shows that while practical tools and interventions may help reduce inappropriate prescriptions, it is unclear whether they help optimize appropriate pharmacy which is often necessary for many patients with HF [88].

Systems Changes

Creating a consolidated, comprehensive, and portable list of medications with their indications will help provide consistency across multiple providers, help ongoing monitoring

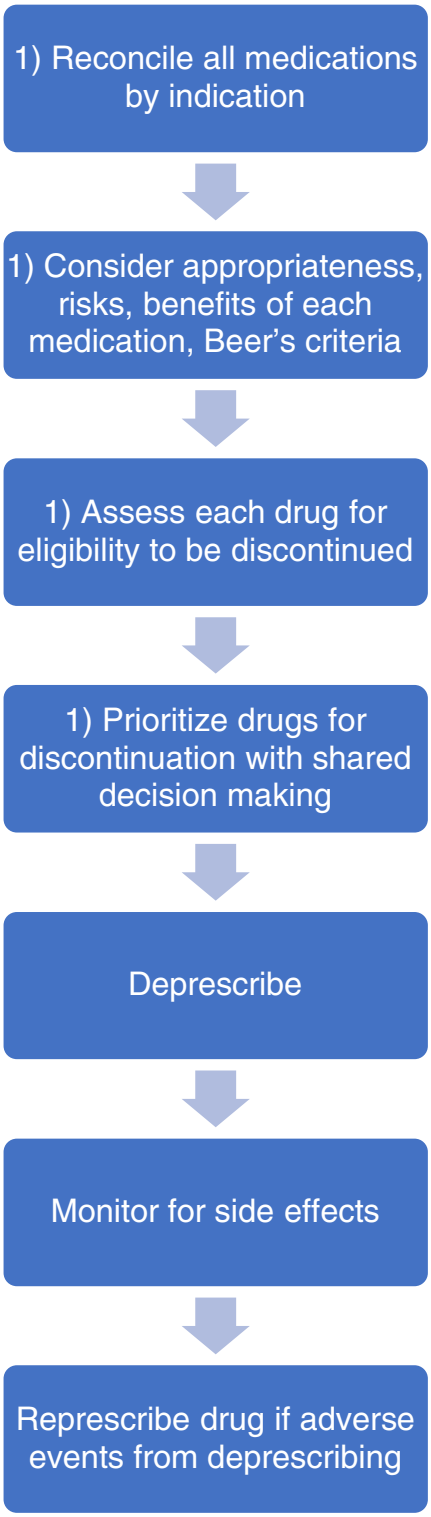

Fig. 4 Geriatrics deprescribing protocol [87] modified to include a final step of re-prescribing medications if and when appropriate

of entire medication regimens, and continuously reassess the appropriateness of various medications [20]. Others have suggested systems changes that will draw attention the number of medications prescribed at every patient encounter, such as a "sixth vital sign" in the electronic medical record, as well as structures to provide time and reimbursement for evaluating polypharmacy [89]. There is also new data that electronic health record (EHR) best practice alerts can be effective and low-cost strategies to increase rates of GDMT prescription for those with HFrEF [90].

Innovative Therapies

While not commonly used in clinical practice, therapies such as a polypill (1 pill containing a fixed dose of multiple medications) may help reduce pill burden for patients [19]. There has been recent promising data on the utility of a polypill for hypertension, showing that a fixed-dose quadruple quarter-dose combination pill achieved and maintained blood pressure better than starting monotherapy [91]. While this strategy does not reduce the absolute number of medication ingredients a patient takes, it is an area of ongoing research that may help mitigate some risks of polypharmacy (such as non-adherence) and reduce side effects of drugs due to the lower dose per drug used.

Role of Cardiologists and HF Specialists in Addressing Polypharmacy

With increasingly subspecialized care for chronic diseases, older adults with HF will need to have their care coordinated across multiple providers, including primary care physicians, cardiologists, HF specialists, nurses, physical therapists, caregivers, and pharmacists (Fig. 3). Some advocate that specialists responsible for managing HF for older adults should not only focus on HF therapy, but also consider quality of life, related comorbidities, and polypharmacy in their therapeutic decision making [8]. If cardiologists and HF specialty teams are providing the most frequent and continuous care for older adults with HF, perhaps there is a role for them to consider not only the indications for HF medications, but for other cardiac and non-cardiac medications and social factors that may interact with HF medications or contribute to poorer outcomes in those with polypharmacy. Figure 5 shows the different layers of health and well-being cardiologists and HF specialists may be able to assess and optimize.

Conclusion

Assessing polypharmacy in older adults with HF is complicated. There is innate tension between the well-studied benefits of optimized HF therapy for older adults that must be weighed against the risks of polypharmacy and the unknowns that still exist [18, 19] (Table 3). A shift in

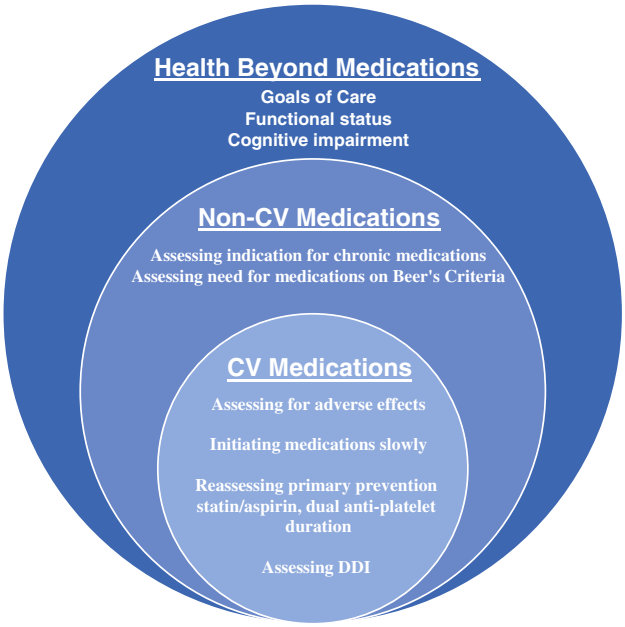

Fig. 5 Different layers of health and well-being all specialists (including cardiologists and HF specialists) may be able to assess, integrate, and optimize for older adults with HF and polypharmacy

paradigm is therefore needed when evaluating polypharmacy in patients with HF; instead of assuming all polypharmacy is "good" or "bad," we advocate for a concerted move to an individualized approach to determine the appropriateness of specific medications [12, 18–20]. Given the overall evidence supporting optimized HF therapies for symptom and mortality benefits, it is clear that polypharmacy in this context can be appropriate and should be viewed differently from "inappropriate" polypharmacy, such as for those on chronic medications without a clear indication. In addition, rather than focusing on a binary numeric threshold of whether or not a patient has polypharmacy, a more nuanced and clinically useful strategy is to critically assess the appropriateness, risks, and benefits of each medication prescribed to a patient to optimize entire medication regimens.

Clinicians should not avoid evidence-based HF regimens that will extend survival and quality of life for the sole purpose of reducing the number of mediations a patient takes. However, advances in evidence-based medical treatments have progressed without corresponding guidance on managing multi-morbidity or the risks of polypharmacy [10]. Beyond the context of HF and cardiology, there is data that adhering to clinical practice guidelines without critically assessing the holistic indications when caring for an older adult with several comorbidities may have unintended effects [92]. Solely basing quality metrics and pay for performance on these guidelines may lead to inappropriate care for complex older adults and incentivize wrong aspects of care, impacting quality of life [92].

Future areas of research are required including studying outcomes of HF medication prescription and deprescription

Table 3 What is known and unknown about polypharmacy and HF

	What is known	What is not known
Polypharmacy	Polypharmacy is ubiquitous among patients with HF Polypharmacy in patients with HF is not always due to HF-related treatments Polypharmacy is associated with disability, hospitalizations, and decreased quality of life	What is a clinically meaningful definition of polypharmacy for patients with HF? How can we most effectively describe medication burden in these patients? How do we weigh these risks against GDMT's benefits (which include increase functional status, decreased hospitalizations, and increased quality of life)?
Generalizability of HF trials to older adults	Adults 65 years old or older were well represented in clinical trials Safety and efficacy of drugs were largely homogenous across age distributions	Are the trials generalizable to those older than 80, the sickest older adults, or those who are frail? Are adverse events worse in routine clinical practice than suggested in the clinical trials?
GDMT for older adults	Individual drugs and multi-drug regimens improve mortality and symptoms	What is the safest way to initiate, sequence, or prioritize medications within this regimen for older adults?
Deprescription	Deprescription strategies might not significantly reduce medication burden or improve outcomes It is important to actively deprescribe inappropriate medications	Are studies on deprescription generalizable to CV or HF medications?
Deprescription of HF treatments	Limited data suggests deprescription of HF treatments leads to disease recurrence and adverse withdrawal effects	Does deprescription of HF treatments improve quality of life, functional status, or mortality in older adults? Is deprescription of HF treatments safe and/or effective?

across subtypes and age subgroups. There is also a need for data on optimal sequencing and prioritization of medications within GDMT. For instance, older adults with orthostatic hypotension may have increased adverse symptoms to BB, ACEi, ARB, or ARNI but may tolerate MRA and SGLT2i better because of their lower hemodynamic profile [19].

While there are also a lack of data and national guidance on how to mitigate the risks of polypharmacy in older adults with optimized HF medical therapy, an individualized approach to these decisions (taking into account goals of care, functional status, and comorbid conditions) with patients and caregivers and multidisciplinary healthcare team members will be crucial. Importantly, the subjective "appropriateness" of polypharmacy dynamically changes over time as goals of care and life situations change with age [12]. For older adults with HF, this means becoming comfortable with allowing for "permissive," but appropriate, polypharmacy.

Declarations

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