

Definition of Polypharmacy in Heart Failure: A Scoping Review of the Literature

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Abstract

Patients with heart failure (HF) have a high prevalence of polypharmacy, which can lead to drug interactions, cognitive impairment, and medication non-compliance. However, the definition of polypharmacy in these patients is still inconsistent. The aim of this scoping review was to find the most common definition of polypharmacy in HF patients. We conducted a scoping review searching Medline, Embase, CINAHL, and Cochrane using terms including polypharmacy, HF and deprescribing, which resulted in 7,949 articles. Articles without a definition of polypharmacy in HF patients and articles which included patients < 18 years of age were excluded; only 59 articles were included. Of the 59 articles, 49% (n = 29) were retrospective, 20% (n = 12) were prospective, 10% (n = 6) were cross-sectional, and 27% (n = 16) were review articles. Twenty percent (n = 12) of the articles focused on HF with reduced ejection fraction, 10% (n = 6) focused on HF with preserved ejection fraction and 69% (n = 41) articles either focused on both diagnoses or did not clarify the specific type of HF. The most common cutoff for polypharmacy in HF was five medications (59%, n = 35). There was no consensus regarding the inclusion or exclusion of over-the-counter medications, supplements, or vitamins. Some newer studies used a cutoff of 10 medications (14%, n = 8), and this may be a more practical and meaningful definition for HF patients.

Keywords: Heart failure; Older patients; Polypharmacy

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Introduction

A high medication burden is remarkably prevalent among patients with heart failure (HF), both in the inpatient and outpatient setting. The prevalence of a high medication burden in HF patients is increasing as patients are living longer with more chronic medical conditions, and new medications are added to guideline-directed medical therapy (GDMT) [1]. This can lead to drug-drug interactions, poor adherence, adverse reactions, cognitive impairment, and decreased medication compliance [2, 3]. A recent study showed that 84% of HF patients were taking ≥ 5 medications on admission, 95% of HF patients were taking ≥ 5 on discharge, and 55% of HF patients were taking ≥ 10 medications on discharge [4]. A high medication burden is often characterized as polypharmacy; however, there are several definitions of polypharmacy in the literature. Some studies define polypharmacy quantitatively, for example, taking ≥ 5 medications, whereas other studies define polypharmacy qualitatively, for example, a complex drug regimen [5, 6]. Although the definition of polypharmacy in HF patients is often debated, most experts agree that polypharmacy is an underestimated problem in this population [2]. The aims of this review were: 1) to conduct a scoping review to find the most common definition of polypharmacy in HF patients, 2) to assess how the literature defined polypharmacy in this specific group, and 3) to review the impact of polypharmacy on patients with HF.

Review Methods

We conducted a scoping review searching Ovid Medline, Elsevier Embase, CINAHL, and Cochrane Library using terms including polypharmacy, HF, and deprescribing, which resulted in 7,949 articles. The search was conducted in March 2021 (Supplementary Material 1, www.cardiologyres.org). The abstracts of all 7,949 articles were screened by two independent reviewers. Of the 7,949 articles, both reviewers independently agreed on including 117 articles and excluding 7,219 articles. The independent reviewers disagreed on 613 articles, and a third independent reviewer resolved these disputes, ultimately deciding to include 384 of the articles. Of the 7,949 articles, 501 articles passed the initial screening phase. The 501 articles were fully examined, and of those, 59 were included (Fig. 1). Abstracts were included if they defined polypharmacy in HF

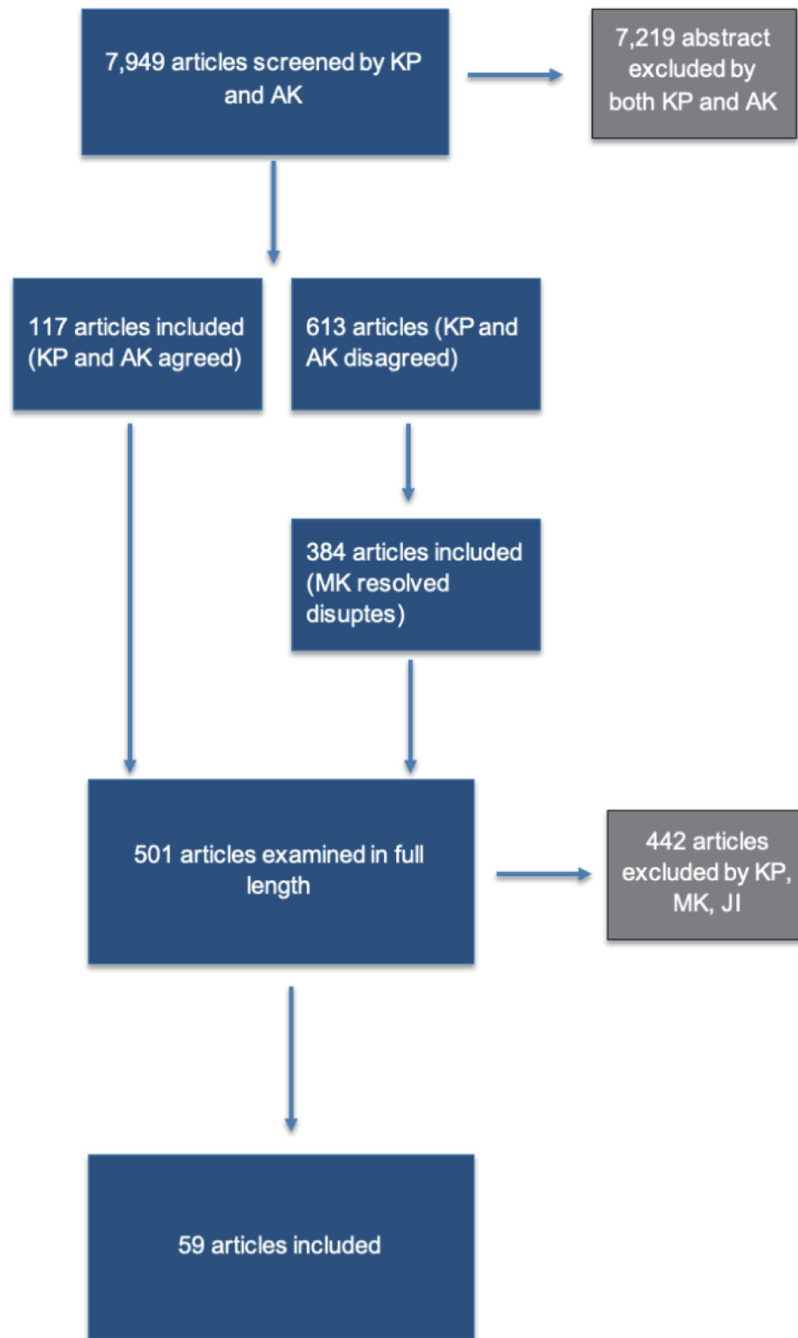


Figure 1. Article selection criteria for the scoping review.

populations and were written in English. Abstracts were excluded if they did not include a definition for polypharmacy in patients with HF or if they included patients < 18 years of age.

Most Commonly Used Definition of Polypharmacy

Of the 59 articles, 48% (n = 29) were retrospective, 20% (n =

12) were prospective, 10% (n = 6) were cross-sectional, and 27% (n = 16) were review articles (Table 1) [2-59]. Of note, some of the articles fit into more than one category. Twenty percent (n = 12) of the articles focused on HF with reduced ejection fraction (HFrEF), 10% (n = 6) focused on HF with preserved ejection fraction (HFpEF), and 69% (n = 41) articles either focused on both diagnoses or did not clarify the specific type of HF. The most common cardiovascular comorbidities identified in these articles were hypertension, diabetes, dys-

Table 1. Articles Used for Scoping Review, Their Definitions, Study Types and Details in the Study

First author, reference	Year published	Definition of polypharmacy in HF patients	What meds did they include or exclude (OTC, vitamins, etc.)?	Article type	Rational for the definition documented	How the definition of polypharmacy used?
Albert [11]	2007	Use of multiple medications in a complex drug regimen	Not identified	Review	Yes	As in the review
Abbas [12]	2015	≥ 5 different prescriptions	Not identified	Retrospective	No	As one of the variables
Barcelo [9]	2014	> 5 daily medications	Not identified	Retrospective	Yes	As one of the outcomes
Baron-Franco [7]	2017	≥ 5 repeat medications	Not identified	Cross-sectional	No	As one of the outcomes
Brinker [13]	2019	≥ 10 medications	Not identified	Retrospective	No	As one of the outcomes
Brinker [14]	2020	≥ 10 medications	Included OTC medications	Retrospective	Yes	As one of the variables
Altunbas [15]	2016	≥ 6 medications taken concurrently	Included all discharge prescriptions	Retrospective	Yes	As one of the outcomes
Alvarez [16]	2019	Polypharmacy ≥ 5 medications, excessive polypharmacy ≥ 10 medications	Included all pharmacy claims	Retrospective	No	As one of the variables
Cobretti [17]	2017	≥ 5 medications	Included OTC medications	Cross-sectional	Yes	As in the review
De Geest [18]	2004	≥ 5 medications simultaneously	Not identified	Review	Yes	As in the review
Eijnsink [19]	2015	≥ 5 prescriptions	Included all medications that were prescribed	Retrospective	No	As one of the variables and also one of the outcomes
El Hadidi [20]	2020	≥ 5 medications	Excluded OTC medications, dietary supplements, herbal medicines	Review	Yes	As in the review
Bader [10]	2017	> 5 medications	Not identified	Review	Yes	As in the review
Bansal [21]	2020	> 5 medications	Included all medications that were prescribed	Prospective and retrospective	Yes	As in the review
Butrous [22]	2016	Chronic use of ≥ 5 medications	Not identified	Review	No	As in the review
Fentie Wendie [23]	2020	Daily consumption of ≥ 5 medications	Included all medications that were prescribed	Prospective	No	As one of the outcomes
Godden [24]	2014	Prescription of multiple medications	Included all medications that were prescribed	Retrospective	No	As one of the outcomes
Goyal [25]	2019	≥ 5 medications	Not identified	Retrospective	Yes	As one of the outcomes
Guirguis [26]	2019	≥ 5 medications	Not identified	Retrospective	No	As in the review
Laroche [27]	2017	Excessive polypharmacy ≥ 10 medications	Not identified	Retrospective	No	As one of the outcomes
Parajuli [28]	2021	Polypharmacy ≥ 5 medications, hyperpolypharmacy ≥ 10 medications	Not identified	Retrospective	Yes	As one of the outcomes
Proietti [29]	2019	≥ 5 medications	Not identified	Retrospective	No	As one of the outcomes
Reed [30]	2014	≥ 4 medications	Not identified	Review	No	As in the review
Rushton [31]	2011	Multiple drug therapies	Not identified	Review	Yes	As in the review
Sritharan [32]	2020	≥ 5 medications	Included OTC medications, supplements, and as-needed medications	Retrospective	No	As one of the outcomes
Ozan [33]	2019	≥ 10 medications	Not identified	Retrospective	No	As one of the outcomes
Unlu [4]	2020	≥ 10 medications	Not identified	Retrospective	No	As one of the outcomes
von Lueder [34]	2014	≥ 4 concomitant drugs	Not identified	Review	No	As in the review

Table 1. Articles Used for Scoping Review, Their Definitions, Study Types and Details in the Study - (continued)

First author, reference	Year published	Definition of polypharmacy in HF patients	What meds did they include or exclude (OTC, vitamins, etc.)?	Article type	Rational for the definition documented	How the definition of polypharmacy used?
Wu [35]	2021	Polypharmacy: use of 5 - 9 medications, hyperpolypharmacy: use of 10 - 14 medications, super hyperpolypharmacy: ≥ 15 medications	Not identified	Retrospective	Yes	As one of the variables
Kleipool [36]	2020	Chronic use of ≥ 5 medications	Not identified	Prospective	Yes	As one of the variables
Knafl [37]	2014	Chronic use of ≥ 5 medications	Not identified	Prospective	Yes	As one of the variables
Kumar [38]	2019	≥ 5 medications	Not identified	Review	Yes	As in the review
Makris [39]	2020	Chronic use of ≥ 10 medications	Not identified	Review	Yes	As in the review
Malouf [40]	2020	≥ 10 medications	Not identified	Retrospective	No	As one of the outcomes
Martinez-Selles [41]	2004	≥ 6 pills	Included OTC medications	Survey	No	As one of the outcomes
Masoudi [42]	2005	Prescription of multiple drugs concurrently	Not identified	Retrospective	Yes	As in the review
Navid [43]	2020	≥ 5 medications	Not identified	Retrospective	No	As one of the variables
Niriayo [44]	2018	≥ 5 medications	Not identified	Prospective	No	As one of the variables
Page 2nd [45]	2016	Long-term use of ≥ 5 medications	Included OTC, complementary and alternative meds	Review	Yes	As in the review
Parmley [46]	2000	Use of 3 - 5 drugs	Not identified	Review	No	As in the review
Rich [5]	2012	Chronic use of ≥ 5 medications	Included OTC medications and supplements	Review	Yes	As in the review
Ruiz-Laiglesia [47]	2016	≥ 5 medications	Not identified	Review	No	As in the review
Harwood [48]	2015	≥ 5 medications	Included vitamins	Prospective	No	As one of the variables
Hornsby [49]	2017	≥ 5 medications	Not identified	Prospective	No	As one of the outcomes
Jenghua [50]	2021	Polypharmacy ≥ 5 medications, hyperpolypharmacy ≥ 10 medications	Not identified	Retrospective and cross-sectional	Yes	As in the review
Rushton [51]	2014	2 or more main drug groups prescribed at the same time	Not identified	Retrospective and cross-sectional	Yes	As one of the outcomes
Salzer [3]	2019	≥ 5 medications	Not identified	Prospective	No	As one of the outcomes
Screver [52]	2017	≥ 5 medications	Not identified	Review	Yes	As in the review
Shikata [53]	2016	Chronic use of ≥ 5 medications	Not identified	Prospective	No	As one of the variables
Sunaga [54]	2020	≥ 6 medications	Included NSAIDs	Retrospective	No	As one of the variables
Wammes [55]	2019	Polypharmacy ≥ 5 prescription medications within a period of 3 months, excessive polypharmacy ≥ 10 prescription medications	Excluded OTC medications	Retrospective	Yes	As one of the variables and also one of the outcomes
Fujita [56]	2019	≥ 7 medications	Not identified	Prospective	No	As one of the variables

Table 1. Articles Used for Scoping Review, Their Definitions, Study Types and Details in the Study - (continued)

First author, reference	Year published	Definition of polypharmacy in HF patients	What meds did they include or exclude (OTC, vitamins, etc.)?	Article type	Rational for the definition documented	How the definition of polypharmacy used?
Georgiev [6]	2019	Complex drug regimen	Not identified	Retrospective	No	As in the review
Unlu [4]	2020	≥ 10 medications	Included multivitamins and electrolyte supplements	Retrospective	No	As one of the outcomes
Haq [57]	2020	Complex drug regimen	Not identified	Retrospective and cross-sectional	No	As in the review
Hopper [58]	2016	≥ 5 medications	Included potassium supplementation	Prospective	No	As one of the outcomes
Kennel [8]	2019	Hyperpolypharmacy ≥ 10 medications	Included topical agents when prescribed, did not include non-prescription medications and dietary supplements	Retrospective and cross-sectional	Yes	As one of the outcomes
Kinugasa [59]	2020	Greater than or equal to the mean number of prescribed medications in the cohort (≥ 8 or more)	Not identified	Prospective	No	As one of the outcomes
Mastromarino [2]	2014	Chronic use of ≥ 5 medications	Not identified	Review	Yes	As in the review

HF: heart failure; NSAIDs: nonsteroidal anti-inflammatory drugs; OTC: over-the-counter.

lipidemia, ischemic heart disease, and atrial fibrillation.

Quantitative definition

The majority of articles defined polypharmacy quantitatively. The most common cutoff for polypharmacy in HF was five medications (58%, n = 35) and the second most common cutoff for polypharmacy in HF was 10 medications (14%, n = 8). Furthermore, several articles also used the definition of hyperpolypharmacy or excessive polypharmacy with a cutoff value of 10 medications, apart from the definition of polypharmacy. Furthermore, one study by Kinugasa et al used the mean number of medications in the study cohort as the definition of polypharmacy [59].

Qualitative definition

Although we planned this review with the aim to identify a quantitative definition of polypharmacy, we recognized that some articles only defined polypharmacy in HF qualitatively (n = 6). For example, the common qualitative definitions included themes such as complex medication regimens and a high medication burden. Also, several studies used both quantitative and qualitative nuance to define polypharmacy such as “the use of multiple medications in a complex drug regimen” or “prescription of multiple drugs concurrently.” This is a finding that we did not expect, but these mixed definitions were commonly used.

Rationale of the definition

While reviewing the literature, we also found that more than half of the articles (55%, n = 33) that we reviewed did not specify their rationale of using such definition of polypharmacy. It reflects that the definition of polypharmacy has been used somewhat arbitrarily by the authors without scientific evidence.

Included medications

Throughout the review, we realized that there was no consensus regarding the inclusion or exclusion of over-the-counter (OTC) medications, supplements, or vitamins. However, the most common medications at both admission and discharge were non-cardiovascular and included proton-pump inhibitors, electrolyte supplements, and multivitamins [4]. There was no consensus regarding the inclusion or exclusion of as-needed medications, medications that were required for a short duration, or chronically prescribed medication.

Why Is Polypharmacy Important

As one of the leading causes of high mortality and morbidity,

HF mainly affects older adults, evidenced by that more than half of patients with HF in the USA are 75 years or older [60]. In the last decade, GDMT for HF has introduced many medications with survival benefits, recommending a combination of multiple medications for optimal management of HF [61-63]. Such combinations of medications have shown clinical benefits in multiple randomized controlled trials, but in the real world, medications also create problems in older adults. These problems include a high prevalence of medication-related issues including medication errors, non-adherence, drug-drug or drug-disease interactions, and adverse drug effects. Such medication-related problems could be associated with adverse clinical outcomes and compromise each medication's expected survival benefit among older adults with HF [64-66]. The patient's pre-existing mental or physical limitations can also intensify the impacts of polypharmacy such as medication errors, non-adherence or prescribing cascade [67-69].

Therefore, identifying polypharmacy and its predicted impact on the pharmacotherapy of HF for older adults is crucial in real-world practice. However, the true impact of polypharmacy may not only come from the number of the medications, but also from other factors in the context of polypharmacy.

Factors to Consider for Appropriate Definition of Polypharmacy

Number of medications

It is obvious that the number of medications should be one of the most important factors to consider. It has been well documented that the number of medications is associated with adverse clinical impact on older adults. For example, a study showed that a person taking five or seven medications has a high risk of adverse drug reactions of 58% and 82% respectively, compared to 13% for a person taking two medications [70].

Regimen complexity

Older adults with HF are not only prescribed many medications, but also instructed to take them with a complex schedule. For example, beta-blockers may be prescribed twice a day, angiotensin-converting enzyme inhibitors once a day and diuretics as needed. Although such complex regimens were proven to be effective collectively, the true benefit of the regimen depends on the patient's adherence [71]. Therefore, when we define polypharmacy, the complexity of regimen also should be accounted for.

Interaction with other medications

When patients have multiple medical conditions, a situation when one medication for one medical condition may be contraindicated for another medical condition may occur (thera-

peutic competition) [72, 73]. Or, the two medications interact with each other to weaken the clinical benefit of one or worsen the side effect of one. Therefore, when we define polypharmacy to assess its impact on patients, consideration of drug-drug interactions should be accounted for [71].

Interaction with other medical conditions

Consideration to pre-existing conditions within older patients who medicate for HF may require greater attention, when discussing polypharmacy. Mental, physical, or other life-influencing hardships may cause a patient to take less than prescribed dosages, alter medication frequencies, or forego consumption completely [7]. For example, dementia will affect the older adult's ability to remember the medication schedule. Physical impairment may affect the older patient's capability to drive to pick up the medications. Or, older adults with other life-threatening medical condition may also decide not to take medications for other medical conditions. Therefore, when defining polypharmacy, such drug-disease interactions, especially drug-geriatric syndromes, should also be considered.

Future direction

In summation, the devising of medication regimens in older patients with HF should be proactive. Accounting for a patient's pre-existing conditions, economic background, and daily support measures are of high significance in mitigating polypharmacy, attempts to manage consequences of polypharmacy after the fact levy further complications for older adults with HF. Unforeseen conflicts with patient comorbidities, ability to begin and maintain medication regimens, and possible contraindications between drugs can be associated with polypharmacy and further impact overall clinical benefit. With polypharmacy more thoroughly defined and considered during pharmacotherapy, patient treatment plans may be optimized and the expected clinical benefit may be maximized [71].

Discussion

From our scoping review, we found out that most studies define polypharmacy in HF quantitatively and the most common cutoff for polypharmacy in HF was five medications (58%, $n = 35$). The second most common cutoff was 10 medications (14%, $n = 8$). Nevertheless, there were many discrepancies on what medications to include. It is unclear if short-term, OTC, or as needed medications should be included in the definition of polypharmacy. It is also unclear if polypills, for example, sacubitril-valsartan, should be counted as one medication or several when defining polypharmacy. Further discussions of polypills when accounting for the polypharmacy should be done, since recent studies have shown that polypills decrease pill burden and may increase compliance by decreasing medication regimen complexity [74].

Another factor that is often not discussed regarding poly-

pharmacy is the frequency of dosing. Providers should be cautious with medications that need to be taken more than once a day. Studies have shown that the number of doses per day is inversely related to compliance [75]. In some cases, what matters more to the patient's compliance could be the frequency of dosing rather than the number of pills. Providers should consider reducing medication frequency whenever appropriate for a simpler medication regime.

Polypharmacy disproportionately affects certain populations, and higher rates of polypharmacy are seen in low socioeconomic status patients. For example, low income and low educational level are independently associated with higher rates of polypharmacy in patients with HF and low-income patients also have lower rates of GDMT, one example of sub-optimal prescribing with both underutilization (lower rates of GDMT) and overutilization of medications (higher rates of polypharmacy) concurrently [8, 76].

Providers should pay close attention to patients with advanced HF [9]. Most HF studies are done on healthier patients, and therefore these medications may not have the same benefit-risk profile with advanced HF and a poor prognosis [10]. These patients should be seen by HF and palliative care specialists. Although palliative care providers may increase polypharmacy in this population, they improve the patient's quality of life [77]. Providers should consider deprescribing prophylactic and life-prolonging medications in advanced HF patients with a limited life expectancy while allowing for "appropriate polypharmacy" and an emphasis on medications that improve quality of life [9, 77]. In appropriate polypharmacy, patients may be taking more than five or 10 medications; however, the medications are appropriate and evidence-based. In appropriate polypharmacy, the benefit of polypharmacy outweighs the risks.

As HF management evolves, the definition of polypharmacy in this patient population may also need to adapt. For example, HF_{rEF} GDMT includes at least four or five different medication classes depending on the patient's condition, including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors. If the HF_{rEF} is secondary to ischemia, antiplatelet and lipid-lowering medications may also be indicated. Additionally, HF patients often have other comorbidities, such as diabetes mellitus and chronic obstructive pulmonary disease, that require treatment with additional medications. If we use the cutoff value of 5 for the definition of polypharmacy, the majority of the HF patients would have polypharmacy, and the distinguishing power of polypharmacy would become low. Therefore, when we define polypharmacy in HF patients, whether we also should include the essential GDMT medications or not becomes a question. However, our review revealed that most of the definitions of polypharmacy used the total number of medications regardless of the classification of the medications. Furthermore, because of the same reason that GDMT itself induces polypharmacy, recognizing that those essential medications are included in polypharmacy is important. When considering discontinuation of medications in HF patients, it may be helpful to view medications in a hierarchical manner based on the patient's comorbidities, focusing on removing medications with little to no benefit, while continuing life prolong-

ing medications. For example, when we consider deprescribing, we should focus on non-GDMT medications first, since GDMT medications are still essential and critical for survival and clinical benefits for HF management.

A recent systemic review also found that the most common definition of polypharmacy in patients with HF was ≥ 5 medications [78]. Our scoping review had several differences compared to Beezer et al, including a larger sample size of 59 articles compared to 22 articles and inclusion of conference abstracts. While the authors agree with us on the need for a consensus definition, they believe it is unclear whether a qualitative or quantitative definition is more appropriate [78]. Based on our scoping review, we argue that a quantitative definition of polypharmacy in HF is more appropriate with a cutoff of ≥ 10 medications.

There are several limitations to this study. We included articles ranging from the years 2000 to 2020. As medication management of HF evolves and new medications are included in GDMT, older articles may not be as relevant. We also excluded any articles that were not published in English, so we may have missed relevant articles. We also included articles regardless of the quality of the study.

Conclusion

In summary, polypharmacy can lead to drug interactions, cognitive impairment, medication non-compliance, and falls. Based on our scoping review, the most common definition of polypharmacy in HF was the use of ≥ 5 medications. Due to the increase in GDMT, life expectancy, and the number of medical comorbidities, most patients with HF use ≥ 5 medications. Although a cutoff of five medications indicates an increased risk of adverse effects, a cutoff of 10 medications captures the highest risk. Increasing the cutoff to 10 medications will emphasize removing unnecessary and harmful medications and preventing discontinuation of beneficial medications. As patients with HF are living longer, providers must be sensitive to geriatric conditions and the risk of adverse events as polypharmacy is common in this population. We agree that providers should pay close attention to those patients taking ≥ 10 medications, but most importantly, providers should make sure that every agent being used has a favorable risk-to-benefit ratio.

Supplementary Material

Suppl 1. Search terms.

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Conflict of Interest

The authors have no conflict of interest to declare.

Author Contributions

KP was involved in the conceptualization, data curation, and original draft preparation. JAI was involved in data curation and editing the draft. AK was involved in data curation and editing the draft. DS was involved in data interpretation and editing the draft. TH was involved in conceptualization, methodology, data curation, reviewing and editing the draft. PG was involved in reviewing and editing the draft. MJK was involved in conceptualization, methodology, data curation, reviewing and editing the draft, and supervision.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

HF: heart failure; GDMT: guideline-directed medical therapy; OTC: over-the-counter

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