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Polypharmacy definition and prevalence in heart failure: a systematic review

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Abstract

Polypharmacy and heart failure are becoming increasingly common due to an ageing population and the rise of multimorbidity. Treating heart failure necessitates prescribing of multiple medications, in-line with national and international guidelines predisposing patients to polypharmacy. This review aims to identify how polypharmacy has been defined among heart failure patients in the literature, whether a standard definition in relation to heart failure could be identified and to describe the prevalence. The Healthcare Database Advanced Search (HDAS) was used to search EMBASE, MEDLINE, PubMed, Cinahl and PsychInfo from inception until March 2021. Articles were included of any design, in patients ≥ 18 years old, with a diagnosis of heart failure; that explicitly define and measure polypharmacy. Data were thereafter extracted and described using a narrative synthesis approach. A total of 7522 articles were identified with 22 meeting the inclusion criteria. No standard definition of polypharmacy was identified. The most common definition was that of "≥ 5 medications." Polypharmacy prevalence was high in heart failure populations, ranging from 17.2 to 99%. Missing or heterogeneous methods for defining heart failure and poor patient cohort characterisation limited the impact of most studies. Polypharmacy, most commonly defined as ≥ 5 medications, is highly prevalent in the heart failure population. There is a need for an internationally agreed definition of polypharmacy, allowing accurate review of polypharmacy issues. Whether an arbitrary numerical cut-off is a suitable definition, rather than medication appropriateness, remains unclear. Further studies are necessary to understand the relationship between polypharmacy with specific types of heart failure and related comorbidities.

Keywords Heart failure · Polypharmacy · Prevalence · Multimorbidity · Medication

Introduction

Polypharmacy is an increasingly common phenomenon, which refers to the use of multiple medications by one individual [1]. There is no universal polypharmacy definition; however, a numerical definition of 5 or more medications daily is commonly referred to [2]. The emergence of polypharmacy has been driven by the growth of an ageing population and the rising epidemic of multimorbidity (i.e., the presence of multiple conditions) [1]. General trends in polypharmacy are increasing worldwide [3]. Polypharmacy can be either appropriate, where medications are prescribed for complex conditions, such as heart failure, or for multiple conditions in circumstances where medicines use has been optimised and are prescribed according to best evidence, or problematic, where medications are prescribed inappropriately or where the intended benefits from the medicines are not realised [4]. However, this is not a static situation; over time, changes to a patient's clinical situation and life circumstances can change the appropriateness of previously sound prescribing decisions.

Heart failure is a common complex clinical syndrome of symptoms and signs caused by structural or functional abnormalities, resulting in an impairment of cardiac output

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[5]. It is typically characterised into two types: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), the first being a mechanistic left ventricular pump problem and the latter often being described as a filling problem due to muscle stiffness reducing left ventricular cavity size or dilation of the left atrium. The treatments of both types differ with HFrEF having a large evidence base for sequential drug therapy to improve outcomes; this is in stark contrast to HFpEF, where there are currently no therapeutic options showing prognostic benefit and symptom control being the only management strategy.

Increasingly, the rise in heart failure is seen as a global public health problem, affecting approximately 26 million people worldwide and resulting in more than one million hospitalisations annually in both the USA and Europe [6]. The high prevalence of heart failure has a high clinical, economic and social impact on individuals and health institutes [1, 7].

Heart failure in the majority of cases is the long-term consequence of complex interwoven comorbidity and therefore, similar to polypharmacy, is exacerbated in the ageing population. Many of these comorbidities, such as coronary heart disease and diabetes, are treated and managed with complex pharmacological regimens. The main interventions for successfully treating heart failure itself are also pharmacological. Diuretics provide symptom relief in all types of heart failure, and in HFrEF medications with prognostic benefit include angiotensin-converting-enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter-2 inhibitors (SGLT2). The emergence of this evidence-base from 1990s and implementation via national [5] and international [8] guidelines has led to improving survival rates amongst heart failure patients [9], predisposing them to appropriate polypharmacy even before taking into consideration treatment for concurrent conditions. Due to these factors, total pill burden and polypharmacy complexity is known to be increasing in heart failure patients over time [10].

Polypharmacy may however also bring unwanted challenges around patient safety and is associated with increased incidence of adverse outcomes including mortality, falls, adverse drug reactions, increased length of stay in hospital and readmission to hospital soon after discharge [2]. A review of polypharmacy in older people confirmed an increase of drug related problems such as drug-drug interactions, hospitalisation and mortality, and that adverse drug reactions were the major cause of hospitalisation in 90% of older patients with polypharmacy [3]. The same review found a decline in physical activity, cognitive ability and poor adherence to medication also resulted from polypharmacy.

The aim of this systematic review was to identify if a standard definition of polypharmacy is used in relation to heart failure patients and to describe the prevalence of polypharmacy in a heart failure population.

Methods

Study design

Reporting of this systematic review conformed to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist [11]. This study was registered with the international database of prospectively registered systematic reviews PROSPERO (identification number CRD42020166677).

Search strategy

The Healthcare Database Advanced Search (HDAS) was used to search EMBASE, MEDLINE, PubMed, Cinahl and PsychInfo by one of the investigators (JB) from their inception until and including March 2021. The search strategy was detailed and comprehensive, incorporating multiple terms, including MeSH terms, relevant to heart failure and polypharmacy (see Table 1). Hand searching of references of the articles reviewed also took place.

Eligibility criteria

Inclusion criteria for the review were studies, of any design and any care setting, in patient's ≥ 18 years old, with a diagnosis of heart failure; that explicitly defined and reported the prevalence of polypharmacy. Exclusion criteria were conference abstracts with no full text, studies in languages other than English and/or studies reported only median/mean values or number of total medications.

Table 1 Search terms used within HDAS database

Polypharmacy	Heart failure
Multiple medication*	Congestive cardiac failure
Multiple drug*	Congestive heart failure
Many medication*	Systolic dysfunction
Many drug*	Diastolic dysfunction
Polymedicine*	Left ventricular impairment
Polytherapy*	Cardiac dysfunction
	Ventricular dysfunction
	Reduced ejection fraction
	Ejection fraction

Study selection

Studies were identified, screened and checked for eligibility. Two independent investigators (JB and PF) screened titles and abstracts against the inclusion criteria; any disagreement was resolved by a third independent reviewer (AH). Following this, full text was reviewed (JB and PF) for inclusion; again, any disagreement was discussed between these investigators (JB and PF) and only resolved by a third independent reviewer if no initial agreement was reached (AH).

Data extraction

Data were extracted (JB) from eligible papers using a narrative synthesis approach in March 2020 and April 2021, whereby a data extraction table was developed (see Table 2). Once the initial data extraction was complete, it was verified by another author (PF) in July 2020 and April 2021. This time lag was due to the coronavirus pandemic.

Critical appraisal

Papers were quality assessed and appraised using Critical Appraisal Skills Programme (CASP) screening tool by the lead researcher in July 2020 and April 2021 (JB) and then verified by a second author in September 2020 and April 2021 (PF). This tool was minor adapted for clarity and to suit the purpose of the review (shown in column headings in Table 3). Papers were not excluded based on quality assessments.

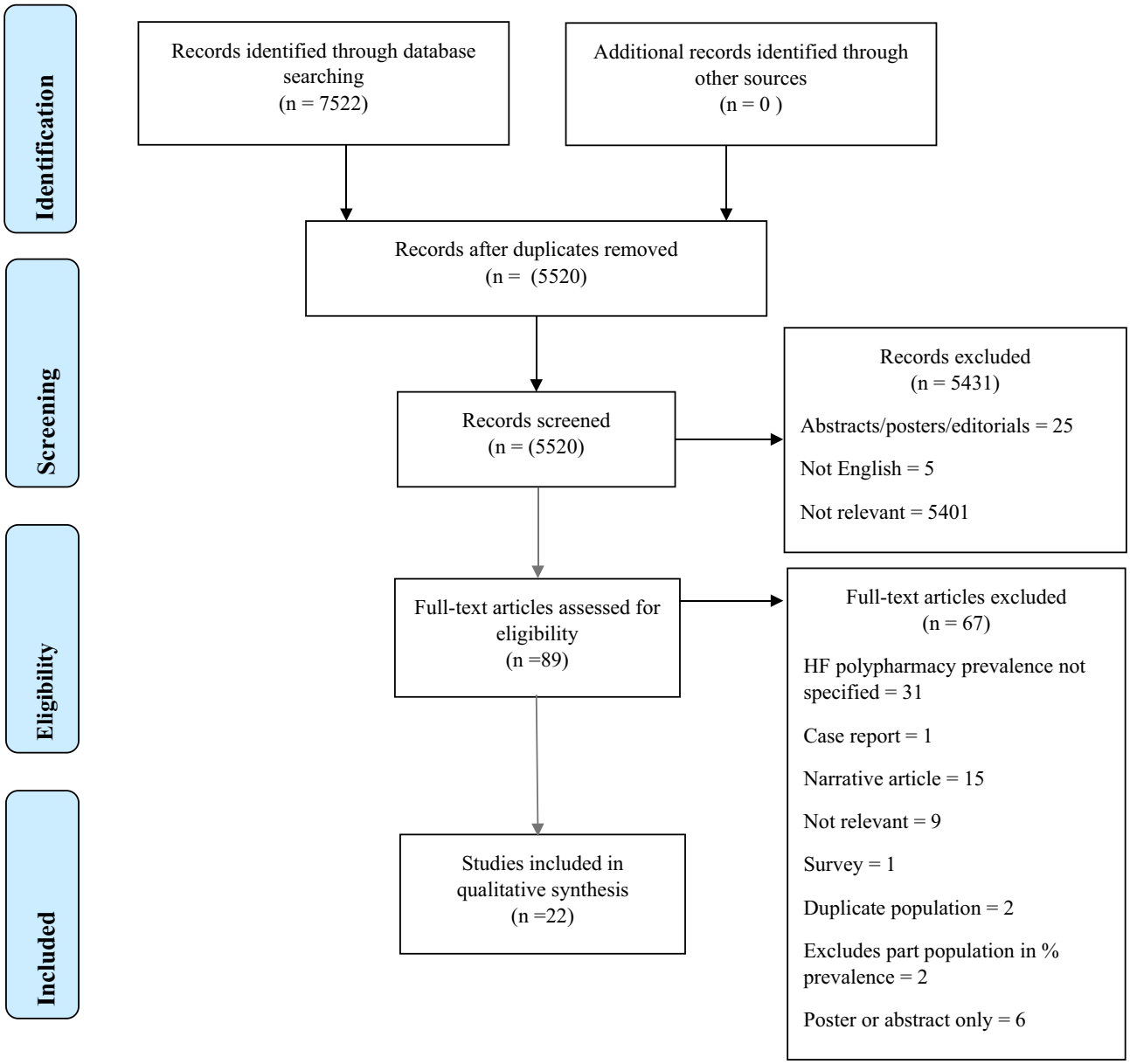

Fig. 1 PRISMA diagram of studies selection

Table 2 Data extraction from included studies

First author	Year of publication	Year(s) of data	Country	Study design	No. of HF patients	Age (mean)	Female %	HF type	Care setting	Relevant inclusion criteria	Relevant exclusion criteria	Prevalence of polypharmacy (%)	Definition of polypharmacy	Number of total medications	Study end points in relation to polypharmacy	Major study limitations
Alvarez P et al	2019	2011–2014	USA	Cohort	40,966	–	36.4	HFrEF; identified from ICD codes on medical claims	Outpatient		Chronic obstructive pulmonary disease on steroids, end-stage renal disease or malignant neoplasm with/without metastatic disease	17.2 3.7	≥ 5 medications ≥ 10 medications	–	Polypharmacy associated with prescribing of potentially harmful drugs in HF population	Younger population; < 64 years No data on association with clinical outcomes (mortality, QoL or health service utilisation) No echocardiogram data Polypharmacy measured at one-time period only
Baron-Franco et al	2017	2007	UK	Cross sectional	17,285	72.3	46.5	LVSD; identified from primary care codes	Primary care	≥ 18 years	HF-PEF	72.3	≥ 5 medications	-	Prevalence of polypharmacy higher in LVSD patients vs. control patients	No data on association with clinical outcomes (mortality, QoL or health service utilisation) No Echocardiogram data Polypharmacy measured at one-time period only
Brinker LM et al	2020	2016–2019	USA	Cross sectional	231	70 median	64	HFpEF	Outpatient	–	–	74	≥ 10 medications	12 median	Prevalence of potentially inappropriate medications was higher when polypharmacy was present in HfpEF patients	No data on association with clinical outcomes (mortality, QoL or health service utilisation) No summarised Echocardiogram data displayed Polypharmacy measured at one-time period only

Table 2 (continued)

First author	Year of publication	Year(s) of data	Country	Study design	No. of HF patients	Age (mean)	Female %	HF type	Care setting	Relevant inclusion criteria	Relevant exclusion criteria	Prevalence of polypharmacy (%)	Definition of polypharmacy	Number of total medications	Study end points in relation to polypharmacy	Major study limitations
Carroll R et al	2016	2008–2013	Australia	Cohort	216	60	23.1	HFrEF; identified by case finding and echocardiogram findings	t			83.7	≥ 5 medications	–	Polypharmacy associated with lack of ACEi dose optimisation	No data on association with clinical outcomes (mortality, QoL or health service utilisation) No summarised Echocardiogram data displayed Polypharmacy measured at one-time period only 25% lost to follow up
Cobretti MR et al	2017	2014–2015	USA	Cross sectional	145	73	35.9	Clinical heart failure (any type); identified from case notes	Outpatient	60–89 years old	Solid organ transplant or HIV	99	≥ 5 medications	13.3 (mean)	Patients with ischaemic aetiology had greater total medication complexity	No data on association with clinical outcomes (mortality, QoL or health service utilisation) No Echocardiogram data No data on HFrEF vs HFpEF Polypharmacy measured at one-time period only

Table 2 (continued)

First author	Year of publication	Year(s) of data	Country	Study design	No. of HF patients	Age (mean)	Female %	HF type	Care setting	Relevant inclusion criteria	Relevant exclusion criteria	Prevalence of polypharmacy (%)	Definition of polypharmacy	Number of total medications	Study end points in relation to polypharmacy	Major study limitations
Goyal P et al	2019	2003–2014	USA	Cross sectional	947	70	49	Self-reported HF (any type)	General population	≥ 50 years	Missing data HF or disability status, or number of medications and those who did not participate in the clinical examination	74	≥ 5 medications	7.2 (mean)	Activities of daily living not associated with polypharmacy	No data on association with clinical outcomes (mortality, QoL or health service utilisation) No Echocardiogram data No data on HFrEF vs HFpEF Polypharmacy measured at one-time period only
Knafl GJ et al	2014	2007–2009	USA	Cross sectional	218	62.8	35.8	Clinical heart failure stage C (any type); based on echo and clinical evidence	Outpatient		Patients with severe depression, dementia, renal failure requiring dialysis, terminal illness, or history of serious drug or alcohol abuse	60.6	≥ 9 medications	9.9 (mean)	Polypharmacy associated with medication non-adherence	No data on association with clinical outcomes (mortality, QoL or health service utilisation) No Echocardiogram data (subanalysis of larger trial without data for this cohort) No data on HFrEF vs HFpEF (subanalysis of larger trial without data for this cohort) Polypharmacy measured at one-time period only

Table 2 (continued)

First author	Year of publication	Year(s) of data	Country	Study design	No. of HF patients	Age (mean)	Female %	HF type	Care setting	Relevant inclusion criteria	Relevant exclusion criteria	Prevalence of polypharmacy (%)	Definition of polypharmacy	Number of total medications	Study end points in relation to polypharmacy	Major study limitations
Lien et al	2002	–	Scotland	Cohort	116	86 (median)	73.3	ICD-10 coded diagnosis of heart failure (any type)	Inpatient	–	–	90	> 4 medications (this is equivalent to ≥ 5 medications)	6 (median)	–	No data on association with clinical outcomes (mortality, QoL or health service utilisation) Incomplete Echocardiogram data Incomplete data on HFrEF vs HFpEF Polypharmacy measured at one-time period only
Martinez-Selles et al	2004	2002	Spain	Cross sectional	65	60.5	24.6	HFrEF; based on case note review	Outpatient	NYHA II–IV Age > 16 years LVEF < 40%	–	74	≥ 6 medications	–	–	Small numbers in study No data on association with clinical outcomes (mortality, QoL or health service utilisation) No summarised Echocardiogram data displayed Polypharmacy measured at one-time period only

Table 2 (continued)

First author	Year of publication	Year(s) of data	Country	Study design	No. of HF patients	Age (mean)	Female %	HF type	Care setting	Relevant inclusion criteria	Relevant exclusion criteria	Prevalence of polypharmacy (%)	Definition of polypharmacy	Number of total medications	Study end points in relation to polypharmacy	Major study limitations
Michalik et al	2013	–	Poland	Cross sectional	26	85.7	89	HF (any type); documented in medical records	Nursing home	Age > 65 years	–	77	≥ 5 medications	9 (median)	Polypharmacy associated with HF in nursing home residents	Small numbers in study No data on association with clinical outcomes (mortality, QoL or health service utilisation) No summarised Echocardiogram data No data on HFrEF vs HFpEF Polypharmacy measured at one-time period only Taken from medical records
Millenaar D et al	2021	2005–2007	USA	Secondary analysis of RCT dataset	5796	–	–	No Info	Outpatient	≥ 65 years	Not on anticoagulation or AF	74	≥ 5 medications (implied)	–	–	No data on association with clinical outcomes (mortality, QoL or health service utilisation) for HF No data on HFrEF vs HFpEF No summarised Echocardiogram data displayed Polypharmacy measured at one-time period only Study not designed specifically for heart failure population

Table 2 (continued)

First author	Year of publication	Year(s) of data	Country	Study design	No. of HF patients	Age (mean)	Female %	HF type	Care setting	Relevant inclusion criteria	Relevant exclusion criteria	Prevalence of polypharmacy (%)	Definition of polypharmacy	Number of total medications	Study end points in relation to polypharmacy	Major study limitations
Mizokami et al	2012	2009	Japan	Cross sectional	266	–	–	No Info	Inpatient	Hospitalisation for any cause	–	60	≥5 medications	6.1 (mean)	Mean medication was the second highest was in patients with congestive heart failure compared to all other conditions	No data on association with clinical outcomes (mortality, QoL or health service utilisation) No Echocardiogram data No data on HFrEF vs HFpEF Polypharmacy measured at one-time period only Study not designed specifically for heart failure population
Niriayo et al	2018	2015–2016	Ethiopia	Cohort	340	50.5	50.3	No info	Inpatient	Recruited into the study during their appointment for medication refilling	Newly diagnosed with HF (<6 months), seriously ill to complete the interview, unwilling to give consent, and their medical record not complete or available for further review	37.9	≥5 medications	4.1 (mean)	Polypharmacy associated with drug therapy problems	No data on association with clinical outcomes (mortality, QoL or health service utilisation) No Echocardiogram data No data on HFrEF vs HFpEF Polypharmacy measured at one-time period only
Nobili A et al	2011	2008	Italy	Cohort	192 (admission) 215 (discharge)	–	–	No info	Inpatient	Age ≥ 65 years Hospitalisation for any cause	Terminal patients	67.2 admission 90.2 discharge	≥5 medications	–	Heart failure was an independent predictor of polypharmacy in admitted patients	No Echocardiogram data No data on HFrEF vs HFpEF Study not designed specifically for heart failure population

Table 2 (continued)

First author	Year of publication	Year(s) of data	Country	Study design	No. of HF patients	Age (mean)	Female %	HF type	Care setting	Relevant inclusion criteria	Relevant exclusion criteria	Prevalence of polypharmacy (%)	Definition of polypharmacy	Number of total medications	Study end points in relation to polypharmacy	Major study limitations
Sganga et al	2015	2010–2011	Italy	Cohort	123	–	–	No info	Inpatient	Consecutive patients admitted to the geriatric and internal medicine acute care wards (any cause)	Age < 65 years	72.4	≥ 8 medications	–	–	No Echocardiogram data No data on HFrEF vs HFpEF Polypharmacy measured at one-time period only Study not designed specifically for heart failure population
Sunaga T et al	2020	2015–2016	Japan	Cross sectional	193	81 median	43.5	Acute decompensated heart failure EF < 40% = 42% EF ≥ 40% = 49.2%	Inpatient	Age ≥ 65 years	< 65 years, those with missing data	66.3	≥ 6 medication	7.1	Polypharmacy is associated with poor prognosis in heart failure patients	Polypharmacy measured at one-time period only
Taylor DM et al	2012	2008–2010	Australia	Cross sectional	359	81.9	57.1	Acute decompensated HF; based on signs and symptoms and patient needing required diuretics/nitrated/morphine/resp support	Inpatient	≥ 18 years Hospital admission with acute HF	Right-sided HF only or acute respiratory distress syndrome	76.9	≥ 5 medications		Polypharmacy is a precipitant of ADHF No difference in polypharmacy prevalence between patients admitted with acute HF and those that developed acute HF while in hospital for another reason	No data on association with clinical outcomes (mortality, QoL or health service utilisation) No Echocardiogram data No data on HFrEF vs HFpEF Polypharmacy measured at one-time period only

Table 2 (continued)

First author	Year of publication	Year(s) of data	Country	Study design	No. of HF patients	Age (mean)	Female %	HF type	Care setting	Relevant inclusion criteria	Relevant exclusion criteria	Prevalence of polypharmacy (%)	Definition of polypharmacy	Number of total medications	Study end points in relation to polypharmacy	Major study limitations
Unlu O et al	2020	2003–2014	USA	Cross sectional	558	76	44	58% HFrEF and 42% HFpEF	Inpatient	≥ 65 years	Hospice referrals; patients without medication lists at admission and discharge	84 admission 95 discharge And 42 admission 55 discharge	≥ 5 medications ≥ 10 medications	–	Polypharmacy in older hospitalised adults rises during admission and over time	No data on association with clinical outcomes (mortality, QoL or health service utilisation) for HF
Verdiani et al	2015	2014	Italy	Cross sectional	770	83.5	55.7	18.3% HFrEF (EF < 35%) 43.1% HFmrEF 38.6% HFpEF (EF > 50%)	Inpatient	Hospitalisation for HF	–	57	≥ 8 medicine classes	–	–	No data on association with clinical outcomes (mortality, QoL or health service utilisation) Incomplete Echocardiogram data Polypharmacy measured at one-time period only
Vrettos I et al	2017	2015–2016	Greece	Cohort	35		–	No info	Inpatient	Age > 65 years Hospitalisation for any cause	–	88.6	≥ 5 medications	–	Heart failure was an independent predictor of polypharmacy in admitted patients	Small numbers in study No data on association with clinical outcomes (mortality, QoL or health service utilisation) No Echocardiogram data No data on HFrEF vs HFpEF Polypharmacy measured at one-time period only Study not designed specifically for heart failure population

Table 2 (continued)

First author	Year of publication	Year(s) of data	Country	Study design	No. of HF patients	Age (mean)	Female %	HF type	Care setting	Relevant inclusion criteria	Relevant exclusion criteria	Prevalence of polypharmacy (%)	Definition of polypharmacy	Number of total medications	Study end points in relation to polypharmacy	Major study limitations
Wawruch M et al	2007	2003–2005	Slovakia	Cross sectional	205	–	–	No info	Inpatient	Age > 65 years Hospitalisation for any cause	Died during admission Missing medical records	71.7	≥ 6 medications	–	Heart failure was an independent predictor of polypharmacy in admitted patients	No data on association with clinical outcomes (mortality, QoL or health service utilisation) No echocardiogram data No data on HFrEF vs HFpEF Polypharmacy measured at one-time period only Not designed specifically for heart failure population
Wu Y et al	2021	2006–2013	USA, Canada Argentina and Brazil	Secondary analysis of RCT dataset	1761	72 median	49.9	HFpEF	Outpatient	≥ 50 years EF ≥ 45%	Severe systemic illness with a life expectancy < 3 years, severe renal dysfunction	93 37.5 35.9 19.6	≥ 5 meds* Polypharmacy 5 – 9 medications Hyperpolypharmacy ≥ 10 -14 medications Super hyperpolypharmacy ≥ 15	–	Polypharmacy is associated reduced risk of all cause death but increased risk of HF hospitalisation	Selected population from total previous clinical trial

ACEi angiotensin converting enzyme inhibitor, *EF* ejection fraction, *ICD* International Classification of Diseases, *HF* heart failure, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HIV* human immunodeficiency virus, *LVSD* left ventricular systolic dysfunction, *PIM* potentially inappropriate medicine, *QoL* quality of life, *UK* United Kingdom, *USA* United States of America

*Combined result to provide ≥ 5 medication

Table 3 Critical appraisal

Adapted CASP tool	Did the study primarily focus on polypharmacy in heart failure?	Were patients identified as heart failure patients in a reasonable way?	Was the exposure to all medications accurately measured to minimise bias?	Was the adjudication of polypharmacy accurately measured to minimise bias?	Have the authors identified all important confounding factors in relation to polypharmacy?	Have they taken account of the confounding factors in the design and/or analysis in relation to polypharmacy?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	What are the polypharmacy results of this study? (%)	How precise are the prevalence results?	Do you believe the results?	Can the results be applied to a local population?	Do the prevalence results of this study fit with other available evidence?	What are the implications of this study for practice?
Alvarez P et al 2019 USA	No; Primary focus was potentially harmful drugs in heart failure	Yes, identified from ICD coding; However, coding data known to be limited as no data an EF	Anticancer drugs excluded Patients with COPD on steroids, end-stage renal disease and/or malignant neoplasms were also excluded, all of which are likely high polypharmacy users	Yes; Polypharmacy defined as ≥ 5 medications Excessive polypharmacy ≥ 10	No; Age inclusion criteria (18–65 years old) not representative of HF general population, women underrepresented (36.4%), uninsured patients not included, and patients needed outpatient and/or inpatient visit during time window, so may not account for chronic stable patients	Not in relation to polypharmacy	N/A (polypharmacy measured at baseline only)	N/A (polypharmacy measured at baseline only)	17.2 (≥ 5 medicines) 3.7 (≥ 10 medicines)	Not displayed	Yes	No, too much confounding and bias	No; Prevalence lower than other studies	Polypharmacy associated with prescription of potentially harmful drugs in heart failure
Baron-Franco et al 2017 UK	Yes (in part); Primary focus was to compare prevalence rates of comorbidity and polypharmacy in those with and without chronic heart failure due to left ventricular systolic dysfunction	Yes, identified from ICD coding; However, coding data known to be limited as no data on EF	Yes, included all repeat medications but may not have included acute medications	Yes; Polypharmacy defined as ≥ 5 medications	Yes; age, sex, socioeconomic deprivation and comorbidity count	Yes; odds ratios for impact of LVSD on polypharmacy standardised for age, sex, deprivation and morbidity count	N/A (cross sectional)	N/A (cross sectional)	72.3	Not displayed	Yes	Yes, large population-level sample with representative age and sex split. Lack of echo data limits findings	Yes	LVSD increases likelihood of polypharmacy compared to controls

Table 3 (continued)

Adapted CASP tool	Did the study primarily focus on polypharmacy in heart failure?	Were patients identified as heart failure patients in a reasonable way?	Was the exposure to all medications accurately measured to minimise bias?	Was the adjudication of polypharmacy accurately measured to minimise bias?	Have the authors identified all important confounding factors in relation to polypharmacy?	Have they taken account of the confounding factors in the design and/or analysis in relation to polypharmacy?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	What are the polypharmacy results of this study? (%)	How precise are the prevalence results?	Do you believe the results?	Can the results be applied to a local population?	Do the prevalence results of this study fit with other available evidence?	What are the implications of this study for practice?
Brinker LM et al 2020 USA	Yes: primary focus was prevalence of polypharmacy in HFpEF	Uncertain; No info on HF diagnosis but has been seen in the preserved ejection fraction clinic	Yes; Taken from electronic medical records only scheduled medications and not as required medication	Yes; Polypharmacy defined as ≥ 10 medications	Yes; described comorbid conditions, well described	No	N/A (polypharmacy measured at baseline only)	N/A (polypharmacy measured at baseline only)	74	Not displayed	Yes	Yes; to a HFpEF population	Yes	Polypharmacy prevalence was high in HFpEF, as were PIM and therapeutic competition
Carroll R et al 2016 Australia	No; Primary focus was prescribing and up-titration of heart failure medications	Yes, secondary analysis of small cohort with echo and clinical findings originally identified for another study	Not described in methods, as not primary focus	Yes Polypharmacy defined as ≥ 5 medications	No; Age not representative of general HF population, women underrepresented and comorbidity index low	Not in relation to polypharmacy	N/A (polypharmacy measured at baseline only)	N/A (polypharmacy measured at baseline only)	83.7	Not displayed	Yes	No, small unrepresentative cohort	Yes	Polypharmacy associated with lack of ACEi dose optimisation
Cobretti MR et al 2017 USA	Yes (indirectly); Primary focus was measuring medication regimen complexity index in heart failure	Uncertain; No info on HF diagnosis but has been seen in the advanced HF clinic	Yes, including OTC Patients with solid organ, transplant or HIV excluded, all of which are likely high polypharmacy users (limitation acknowledged by authors)	Yes Polypharmacy defined as > 5 medications	Yes (indirectly); age, heart failure aetiology, NYHA functional class, and sex	Yes (indirectly)	N/A (cross sectional)	N/A (cross sectional)	99	Not displayed	Yes	Yes, in older adults (60–89 years)	Yes	Patients with ischaemic aetiology had greater total medication complexity but age, sex and NYHA class not associated

Table 3 (continued)

Adapted CASP tool	Did the study primarily focus on polypharmacy in heart failure?	Were patients identified as heart failure patients in a reasonable way?	Was the exposure to all medications accurately measured to minimise bias?	Was the adjudication of polypharmacy accurately measured to minimise bias?	Have the authors identified all important confounding factors in relation to polypharmacy?	Have they taken account of the confounding factors in the design and/or analysis in relation to polypharmacy?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	What are the polypharmacy results of this study? (%)	How precise are the prevalence results?	Do you believe the results?	Can the results be applied to a local population?	Do the prevalence results of this study fit with other available evidence?	What are the implications of this study for practice?
Goyal P et al 2019 USA	Yes; Primary focus was to determine link between number of medicines and functional impairment	Uncertain; self-reported heart failure, so limited data	Yes	Yes Polypharmacy defined as > 5 medications	Yes; ADL impairment, age, sex, race, source of health insurance, education, income, marital status, living alone, access to care, comorbidity count, smoking status, health change from previous year, hypoalbuminemia, memory, number of contacts with healthcare system, and number of hospitalizations	Yes; Performed multivariate regression to look at association between medication count and functional impairment	N/A (cross sectional)	N/A (cross sectional)	74	Not displayed	Yes	Unknown, as self-reported heart failure so results limited	Yes	Activities of daily living not associated with polypharmacy in heart failure

Table 3 (continued)

Adapted CASP tool	Did the study primarily focus on polypharmacy in heart failure?	Were patients identified as heart failure patients in a reasonable way?	Was the exposure to all medications accurately measured to minimise bias?	Was the adjudication of polypharmacy accurately measured to minimise bias?	Have the authors identified all important confounding factors in relation to polypharmacy?	Have they taken account of the confounding factors in the design and/or analysis in relation to polypharmacy?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	What are the polypharmacy results of this study? (%)	How precise are the prevalence results?	Do you believe the results?	Can the results be applied to a local population?	Do the prevalence results of this study fit with other available evidence?	What are the implications of this study for practice?
Knafl GJ et al 2014 USA	No; Primary focus was predictors of non-adherence in heart failure	Yes, diagnosis based on echo findings and symptoms/clinical features	Yes Patients with severe depression, dementia, renal failure requiring dialysis, terminal illness, or history of serious drug or alcohol abuse were excluded, all of which are likely high polypharmacy	Yes Polypharmacy defined as > 9 medications	Yes; Demographics, social support, comorbidity number, blood pressure, symptoms and cognition	Yes; Performed multivariate regression to look at association between many factors, including polypharmacy, and medication adherence	N/A (cross sectional)	N/A (cross sectional)	60.6	Not displayed	Unknown. Patient number not consistent across all analysis	No, many chronic conditions excluded so therefore not representative	Yes	Polypharmacy puts patients at risk of poor compliance
Lien et al 2001 Scotland	Yes (in part); Primary focus was quantify symptoms, comorbidities and polypharmacy in heart failure	Yes, identified from ICD-10 coded diagnosis of heart failure any type; however, coding data known to be limited as no data an EF	Yes	Yes (indirectly) Polypharmacy indirectly defined as > 4 medications	No	Not in relation to polypharmacy	N/A (polypharmacy measured at baseline only)	N/A (polypharmacy measured at baseline only)	90	Not displayed	Yes	Yes, but lack of echo data limits findings	Yes	Heart failure in older patients compounded by major illness and polypharmacy

Table 3 (continued)

Adapted CASP tool	Did the study primarily focus on polypharmacy in heart failure?	Were patients identified as heart failure patients in a reasonable way?	Was the exposure to all medications accurately measured to minimise bias?	Was the adjudication of polypharmacy accurately measured to minimise bias?	Have the authors identified all important confounding factors in relation to polypharmacy?	Have they taken account of the confounding factors in the design and/or analysis in relation to polypharmacy?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	What are the polypharmacy results of this study? (%)	How precise are the prevalence results?	Do you believe the results?	Can the results be applied to a local population?	Do the prevalence results of this study fit with other available evidence?	What are the implications of this study for practice?
Martinez-Selles et al 2003 Spain	Yes; Primary focus was to evaluate the occurrence and patient knowledge of polypharmacy in heart failure	Yes, identified from attendance at HF clinic due to HFrEF (EF < 40%)	Unclear from data collection form in appendix. Data also patient reported which is limited	Yes Polypharmacy defined as > 6 medications	No; age not representative of general HF population and women underrepresented	No	N/A (cross sectional)	N/A (cross sectional)	74	Not displayed	Yes	No, small unrepresentative cohort	Yes	HF patients are commonly on polypharmacy but have poor knowledge about why they take them
Michalik et al 2013 Poland	Yes (in part); was to determine the relationship between HF, coexisting diseases, and use of medications in patients of advanced age living in nursing homes	Uncertain; HF recorded in medical record but incomplete information on type or confirmation	Unclear from methods	Yes Polypharmacy defined as ≥ 5 medications	No	Not in relation to polypharmacy	N/A (cross sectional)	N/A (cross sectional)	77	Not displayed	Yes	Unknown, small nursing home cohort	Yes	HF patients in nursing homes more likely to have polypharmacy than those without HF
Millenaar D et al 2021 USA	No; Primary focus was polypharmacy in AF on long-term anticoagulation	Uncertain; No info on how heart failure was diagnosed	Unclear from methods	Yes; categorised to ≤ 4 medications 5–8 medications and ≥ 9 medications	Yes; age, BMI, CrCl, gender, AF type, ethnicity, HTN, stroke, coronary artery disease, previous MI, Diabetes, valvular heart disease and baseline medications	Yes; adjusted in multivariate analysis	Yes	Yes	74	Not displayed	Yes	Unknown, as uncertain heart failure diagnosis so results limited	Yes	Polypharmacy in AF population is associated increased adverse cardiovascular and bleeding event. No implications for heart failure

Table 3 (continued)

Adapted CASP tool	Did the study primarily focus on polypharmacy in heart failure?	Were patients identified as heart failure patients in a reasonable way?	Was the exposure to all medications accurately measured to minimise bias?	Was the adjudication of polypharmacy accurately measured to minimise bias?	Have the authors identified all important confounding factors in relation to polypharmacy?	Have they taken account of the confounding factors in the design and/or analysis in relation to polypharmacy?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	What are the polypharmacy results of this study? (%)	How precise are the prevalence results?	Do you believe the results?	Can the results be applied to a local population?	Do the prevalence results of this study fit with other available evidence?	What are the implications of this study for practice?
Mizokami et al 2012 Japan	Yes (in part); The objective of this study was to analyse each common disease in the elderly with respect to prescribed drugs and polypharmacy (not all patients had heart failure)	Uncertain; No info on how heart failure was diagnosed	Yes	Yes Polypharmacy defined as ≥ 5 medications	?No. Age, sex and Charleston comorbidity index	No	N/A (cross sectional)	N/A (cross sectional)	60	Not displayed	Yes	Unknown, as uncertain heart failure diagnosis so results limited	Yes	Polypharmacy prevalence was the third highest out of thirteen conditions, after stroke and depression, in patients with congestive heart failure compared to all other conditions
Niriayo et al 2018 Ethiopia	Yes (indirectly); Primary focus was factors contributing to drug therapy problems in HF	Uncertain; No info on how heart failure was diagnosed	Unclear from methods	Yes Polypharmacy defined as ≥ 5 medications	Yes; Gender, age, geography, health beliefs, medication availability, hospitalisation history, aetiology of HF, duration of HF and polypharmacy	Yes (indirectly); multivariate regression to look at factors associated with drug related problems	N/A (polypharmacy measured at baseline only)	N/A (polypharmacy measured at baseline only)	37.9	Not displayed	Yes	No; Very young heart failure cohort from third-world country	No; Lower prevalence, (? younger age group/third world country)	Patients with polypharmacy likely to experience drug therapy problem

Table 3 (continued)

Adapted CASP tool	Did the study primarily focus on polypharmacy in heart failure?	Were patients identified as heart failure patients in a reasonable way?	Was the exposure to all medications accurately measured to minimise bias?	Was the adjudication of polypharmacy accurately measured to minimise bias?	Have the authors identified all important confounding factors in relation to polypharmacy?	Have they taken account of the confounding factors in the design and/or analysis in relation to polypharmacy?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	What are the polypharmacy results of this study? (%)	How precise are the prevalence results?	Do you believe the results?	Can the results be applied to a local population?	Do the prevalence results of this study fit with other available evidence?	What are the implications of this study for practice?
Nobili A et al 2011 Italy	Yes (in part); Primary focus was evaluating the prevalence and factors associated with polypharmacy and investigated the role of polypharmacy as a predictor of length of hospital stay and in-hospital mortality (not all patients had heart failure)	Uncertain; No info on how heart failure was diagnosed	Yes	Yes Polypharmacy defined as ≥ 5 medications	Yes; Demographics, diagnoses, comorbidity, and in-hospital adverse events	Yes (in part); multivariate regression to look at factors associated with polypharmacy and outcomes	5.6% excluded analysis incomplete data 177 patient discharge meds not include—all accounted for as transferred to another facility	Yes	67.2 admission 90.2 discharge	Not displayed	Yes	Unknown, as uncertain heart failure diagnosis so results limited	Yes	Heart failure was an independent predictor of polypharmacy in admitted patients
Sganga et al 2015 Italy	No; Primary focus was to assess whether polypharmacy was associated with an increased rate of rehospitalisation and mortality in elderly patients admitted to hospital	Uncertain; No info on how heart failure was diagnosed	Unclear from methods	Yes Polypharmacy defined as ≥ 8 medications	Yes; Association between outcomes and polypharmacy adjusted for age, sex, Charlson Comorbidity Index, ischemic heart disease, heart failure, Parkinson's disease and diabetes	Not in relation to polypharmacy prevalence	N/A (polypharmacy measured at baseline only)	N/A (polypharmacy measured at baseline only)	72.4	Not displayed	Yes	Unknown, as uncertain heart failure diagnosis so results limited	Yes	Polypharmacy is common in elderly patients admitted to hospital

Table 3 (continued)

Adapted CASP tool	Did the study primarily focus on polypharmacy in heart failure?	Were patients identified as heart failure patients in a reasonable way?	Was the exposure to all medications accurately measured to minimise bias?	Was the adjudication of polypharmacy accurately measured to minimise bias?	Have the authors identified all important confounding factors in relation to polypharmacy?	Have they taken account of the confounding factors in the design and/or analysis in relation to polypharmacy?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	What are the polypharmacy results of this study? (%)	How precise are the prevalence results?	Do you believe the results?	Can the results be applied to a local population?	Do the prevalence results of this study fit with other available evidence?	What are the implications of this study for practice?
Sunaga T et al 2020 Japan	No; Primary focus was associations of all-cause mortality and potentially inappropriate medications	Uncertain; identified from hospital admission not clear if HF admission	Yes Medication list completed by pharmacists on admission	Yes Polypharmacy defined as ≥ 6 medications	Yes; Alb (< 3.5 g/dL), hypertension, chronic obstructive pulmonary disease (COPD), SBP (< 100 mm Hg), number of medication (≥ 6), and NSAIDs	Yes	N/A (cross sectional)	N/A (cross sectional)	66.3	Not displayed	Yes	Yes	Yes	Polypharmacy is associated with poor prognosis
Taylor DM et al 2012 Australia	No; Primary focus was the precipitants of acute decompensated heart failure	Uncertain; Patients required signs and symptoms of heart failure and treatment with diuretics, nitrates, morphine or respiratory support (no info on EF)	Unclear from methods	Yes Polypharmacy defined as ≥ 5 medications (NB– described as > 4 in paper)	No	No	N/A (cross sectional)	N/A (cross sectional)	76.9	Not displayed	Yes	Unknown, as uncertain heart failure diagnosis so results limited	Yes	No difference in polypharmacy prevalence between patients admitted with acute HF and those that developed acute HF while in hospital for another reason

Table 3 (continued)

Adapted CASP tool	Did the study primarily focus on polypharmacy in heart failure?	Were patients identified as heart failure patients in a reasonable way?	Was the exposure to all medications accurately measured to minimise bias?	Was the adjudication of polypharmacy accurately measured to minimise bias?	Have the authors identified all important confounding factors in relation to polypharmacy?	Have they taken account of the confounding factors in the design and/or analysis in relation to polypharmacy?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	What are the polypharmacy results of this study? (%)	How precise are the prevalence results?	Do you believe the results?	Can the results be applied to a local population?	Do the prevalence results of this study fit with other available evidence?	What are the implications of this study for practice?
Unlu O et al 2020 USA	Yes; Primary focus was polypharmacy in heart failure	Yes; Adjudicated by 2 expert clinicians to determine if reason for hospitalisation included exacerbation for HF	Yes; medications taken from medicines reconciliation notes in records	Yes; Polypharmacy defined as ≥ 5 and ≥ 10 medications	Yes	Yes;	N/A (polypharmacy measured on admission and discharge only)	N/A (polypharmacy measured on admission and discharge only)	≥ 5 medications 84 (admission) and 95 (discharge) ≥ 10 medications 42 (admission) and 55 (discharge)	Not displayed	Yes	Yes	Yes	Polypharmacy is common in heart failure patients, increases during admission and is increasing over time
Verdiani et al 2015 Italy	No; Primary focus was to analyse the differences of the HF management in relation to the most recent guidelines	Yes; Patients admitted to hospital characterised into HF types (HFrEF, HFmrEF and HFpEF)	Unclear from methods	Yes; Polypharmacy defined as ≥ 8 medicine classes of medication	No	Not in relation to polypharmacy	N/A (polypharmacy measured at discharge only)	N/A (polypharmacy measured at discharge only)	57	Not displayed	Yes	Yes	Yes but difficult to directly compare as definition of polypharmacy not studied elsewhere	Multiple classes of medication common
Vrettos I et al 2017 Greece	No; Primary focus was to identify the prevalence and the predictors of polypharmacy among consecutively unplanned admissions of patients aged ≥ 65 years (not all patients had HF)	Uncertain; No info on how heart failure was diagnosed	Yes	Yes; Polypharmacy defined as ≥ 5 medications	Yes; Sociodemographic characteristics and across patients' medical and medication history	Yes; Performed multivariate regression to look at factors association with polypharmacy	N/A (cross sectional)	N/A (cross sectional)	88.6	Not displayed	Yes	Unknown, as uncertain heart failure diagnosis so results limited	Yes	Heart failure was an independent predictor of polypharmacy in admitted patients

Table 3 (continued)

Adapted CASP tool	Did the study primarily focus on polypharmacy in heart failure?	Were patients identified as heart failure patients in a reasonable way?	Was the exposure to all medications accurately measured to minimise bias?	Was the adjudication of polypharmacy accurately measured to minimise bias?	Have the authors identified all important confounding factors in relation to polypharmacy?	Have they taken account of the confounding factors in the design and/or analysis in relation to polypharmacy?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	What are the polypharmacy results of this study? (%)	How precise are the prevalence results?	Do you believe the results?	Can the results be applied to a local population?	Do the prevalence results of this study fit with other available evidence?	What are the implications of this study for practice?
Wawruch M et al 2007 Slovakia	No; Primary focus was analyse the prevalence of polypharmacy in a group of older patients; evaluate the influence of hospital stay on the number of drugs taken (not all HF patients)	Uncertain; No info on how heart failure was diagnosed	Yes	Yes; Polypharmacy defined as ≥ 6 medications	Yes; demographics, clinical characteristic, comorbidity and polypharmacy	Yes; Performed multivariate regression to look at factors association with polypharmacy	N/A (cross sectional)	N/A (cross sectional)	71.7	Not displayed	Yes	Unknown, as uncertain heart failure diagnosis so results limited	Yes	Heart failure was an independent predictor of polypharmacy in admitted patients
Wu y et al 2021 China	Yes: Primary focus was the influence of polypharmacy in patients with HFpEF	Yes; Previously identified as HFpEF as per TOPCAT trial	Yes; Medications taken from baselines screening in original study	Yes; Polypharmacy defined as ≥ 5–9 medications Hyperpolypharmacy ≥ 10–14 Super Hyperpolypharmacy ≥ 15 medications	Yes; Extensive list of potential cofounders listed	Yes	Yes	Yes; Mean follow up time 3.3 years	93* 37.5 (5–9 medicines) 35.9 (10–14 medicines) 19.6 (≥ 15 medicines)	Not displayed	Yes	Yes; to a HFpEF population	Yes	Polypharmacy in HFpEF is associated with increased risk of hospitalisation but decreased risk of all cause death

CASP Critical Appraisal Skills Programme, *COPD* chronic obstructive pulmonary disease, *EF* ejection fraction, *HF* heart failure, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *N/A* not applicable, *NB* nota bene, *UK* United Kingdom, *USA* United States of America

*Combined result to provide ≥ 5 medication

Ethics

Ethical approval was not required.

Results

A total of 7522 articles were identified, of which 88 were included for full-text review, 18 were initially included by both independent reviewers (JB and PF), and a further 4 were included after discussion and agreement (JB and PF); 22 articles met the final inclusion criteria and no articles needed adjudication by the third independent reviewer. Figure 1 shows the flow of studies selection according to the PRISMA checklist.

The included studies were all observational in nature and consisted of 7 (41.2%) cohort studies [12–18], 13 (58.8%) cross-sectional studies [19–31], and 2 studies were secondary analyses from previous randomized controlled trial datasets [32, 33]. In total, 70,695 heart failure patients were included in the studies. The mean age of heart failure patients (based on 11 studies [13, 15, 19–24, 26, 27, 31]) was 72.3 years, and 40.3% were female (based on 16 studies [12–15, 19–24, 26, 27, 29–32]).

Studies were across a range of care settings: 8 from outpatients clinics [12, 13, 22, 23, 30, 32–34], 11 from hospital inpatients [14–18, 25–29, 31] and 1 from each general population [21], nursing homes [24] and primary care[19]. Studies were from across the globe: 7 from USA [12, 21, 22, 30, 31, 33, 34]; 3 from Italy [16, 18, 27]; 2 from the UK [14, 19], Japan [25, 29] and Australia [13, 26]; 1 each from of Spain [23], Poland [24], Ethiopia [15], Greece [17] and Slovakia [28] and 1 from north and south America combined [32].

The data collection time frames for studies included in this review range from 2002 to 2019, with only one study collecting data up to 2019 [30]; the majority predate the most recent heart failure evidence and guidelines (ESC 2016 [8] and NICE 2018 [5]) for the sequential additions of drug therapies. New evidence beyond the addition or ACEi/ARB, BB and MRA emerged in 2010 with ivabradine [35], sacubitril/valsartan in 2014 [36] and dapagliflozin in 2019 [37]. As such, 18 of the 22 studies had completed data collection prior to 2015 [14, 16, 18, 19, 22, 23, 25, 26, 28] and all data collected but 1 study preceded the end of 2016 [30].

Comorbidity data, specific to the heart failure patients within the study, were displayed in 5 out of 17 studies [14, 15, 19, 24, 27], and 2 studies report the number of comorbidities [21, 22]. Individual medication class data, specific to the heart failure patients within the study, were displayed in 7 [12, 14, 15, 21, 24, 26, 27] out of 17 studies, and 8 studies [14, 19–25] report the total number of medicines. Although the average number of medicines was not part of the inclusion criteria, some studies reported this, with average number of medicines ranging from 4.1 [15] to 13.3 [34].

A total of 4 studies [12, 13, 19, 23] included an exclusively HFrEF population although no ejection fraction data was available; 2 studies included an exclusively HFpEF population [30, 32], 2 studies[26, 34] included clinical heart failure and 1 study [21] included self-reported heart failure. A study by Verdiani et al. [27] looked at the European Society of Cardiology definition of heart failure and included all 3 groups [8]. Lien et al. [14] Michalik et al. [24] and Unlu et al. [31] included all heart failure, Taylor et al. [26] and Sunaga et al. [29] included all decompensated heart failure admitted to hospital, and the remaining 6 studies did not specify the heart failure cohort included [15–17, 25, 28, 33]. See Table 2 for full data extraction.

Definition of polypharmacy

No standardised definition was used consistently across all the studies. The most commonly used definition was that of 'five or more medications' used in 13 studies [12–17, 19–21, 24–26, 33]. Two studies by Verdiani et al. and Sganga et al. defined polypharmacy as the use of eight or more medications [18, 27] and three used a definition of six or more medications [23, 28, 29]. Knafl et al. [22] chose greater or equal to nine medication as the polypharmacy definition. A definition of excessive polypharmacy, greater or equal to 10 medications, was described by Alvarez et al. [12], Brinker et al. [30] and Unlu et al. [31]. Wu et al. described polypharmacy as 5–9 medications, 10–14 as hyperpolypharmacy and ≥ 15 as super hyperpolypharmacy [32].

Prevalence of polypharmacy

The prevalence of polypharmacy ranged from 17.2% [12] to 99% [17], with 19 of the 22 studies (86%) having polypharmacy > 60%. Where polypharmacy was defined as 5 or more medicines, with 11 out of 13 of these studies finding a prevalence of ≥ 60%. Polypharmacy prevalence was 66.3% [29] to 74% [23, 33] in patients taking six or more medications. Verdiani et al. showed that 57% of patients had eight or more medication classes [27] where Sganga et al. [18] showed 72.4% to be taking eight or more and Knafl et al. having 60.6% taking nine or more medications [22]. In the most recent dataset study, Brinker et al. [30] showed polypharmacy prevalence of ≥ 10 medicines to be 74%, where in an earlier dataset, Unlu et al. [31] found it to be 42% on admission to hospital and 55% at the point of discharge. Wu et al. found 37.5% to have polypharmacy, 35.9% hyperpolypharmacy and 19.6% to have super hyperpolypharmacy.

Quality of evidence

All included studies were appropriately observational in design. All but two of the studies [16, 31] looked at polypharmacy at one particular time point within the study and the patient journey, and therefore, the assessment of completeness of follow up and length of follow up was not applicable. This type of cross-sectional view limits any analysis on association with polypharmacy prevalence and predictors and also stops any analysis of association between polypharmacy and outcomes over time.

In the majority of cases, polypharmacy was not the primary focus of studies. Of the 22 studies, only 6 were designed a priori to address polypharmacy in a heart failure population [14, 20, 22, 30–32]. The remaining 16 studies were designed primarily to address other questions, but collected data for heart failure patients and polypharmacy prevalence by proxy. Little, therefore, is known about how polypharmacy changes over time and in different phases of the heart failure journey (e.g. diagnosis, stable phases, unstable phases and end of life).

The definition of heart failure was highly variable across the studies limiting their impact and generalisability; diagnostic ejection fraction entry criteria was only used in 6 studies [12, 13, 19, 23, 27, 32], and summarised echo findings were only displayed in the studies by Verdiani et al. [27], Unlu et al. [31] and Sunaga et al. [29]. Three studies [12, 14, 19] used coding data to identify heart failure cases and although this is an acceptable way to recruit patients, it limits the ability of the reader differentiation between the types of heart failure and applies the findings. Entry criteria and/or summarised baseline characteristics for the clinical manifestation of the syndrome, for example clinical fluid overload or New York Heart Association class, were only displayed in 4 studies [20, 22, 26, 32]. The type and severity of heart failure often dictate pharmacological treatment, and therefore, these missing data make the clinical understanding and generalisability of the findings difficult to interpret.

Bias on the exposures to all medications was common in many studies, with comorbidity, which impacts on polypharmacy commonly excluded from studies [12, 15, 16, 20, 22, 32], poor definition of how medication histories were collected [13, 15, 23, 24, 26] and uncertainty over whether acute medications and 'over-the-counter' therapies were included [19, 30]. Small sample size in some studies (e.g. 7 studies having < 200 patients [14, 17, 18, 20, 23, 24, 29]) may increase the liability of confounding factors. Participant age was often less than population heart failure cohorts (e.g. 6 studies had mean ages or entry criteria < 65 years of age [12, 13, 15, 18, 22, 23]); the two studies with the lowest prevalence findings were both in younger cohorts.[12, 15]. Comparatively, in the 5 studies using the polypharmacy definition of ≥ 5 medications, where the mean age was above 60, prevalence was higher (range 72–99%).

Women were commonly under-represented with less than 40% female populations in 5 [12, 13, 20, 22, 23] out of 12 studies that displayed data. The study by Alvarez et al. only enrolled patients from an insured cohort [12] and studies by Caroll et al. [13], Millenaar et al. [33] and Wu et al. [32] involved a secondary analysis of previous datasets, both meaning that findings may not be representative of true population-level findings.

Findings from the studies suggest that heart failure and/or LVSD was associated with an increased prevalence of polypharmacy in many cohorts, including the general population [21], patients admitted to hospital [14–18, 25–28] and nursing home patients [24]. Prevalence was also high in outpatients with HFpEF [30, 32]. An ischaemic aetiology was also shown to be associated with polypharmacy in heart failure [20]. Polypharmacy was linked with various types of problem or harm in patients, including the inappropriate prescribing of potentially harmful medications [12, 30], an increased rate of drug therapy problems [15, 30] and poor medication adherence [22] and associated with poor prognosis [29] and heart failure hospitalisations [32]. However, the generalisability and impact of all of these findings are limited due to the heterogeneity of definitions of heart failure, the characterisation of participants and high levels of confounding risk.

Discussion

The results of this systematic review showed variations of the definition of polypharmacy although five or more medications were the predominant definition throughout the studies with data collection from 2002 to 2019, the majority of which predate the most recent drug therapy evidence. This is consistent across the literature, a recent systematic review of polypharmacy definitions found 138 definitions for polypharmacy from 110 articles, the most common of which was the use of five or more medications [2].

Polypharmacy, by any definition, was present in the majority of studies within our review. This ultimately should not be unexpected, as the guideline-based medication interventions recommended for the treatment of heart failure puts patients at risk of polypharmacy, before taking into consideration treatment for comorbid conditions [8]. All of the studies in this review pre-date the evidence base for ARNI and SGLT2 inhibitors, except one[30] where the population was HFPEF and the evidence base for treatment lies with diuretics management and optimal treatment of comorbid conditions. Essentially, all optimised HFrEF patients in 2020, able to tolerate treatment, will typically meet the polypharmacy criteria for 5 or more medications.

While the trend of non-cardiovascular comorbidities among hospitalised patients with heart failure has been increasing over time[23] and is associated with negative outcomes and a growing burden of non-CVD prescriptions, it is unclear whether the high polypharmacy prevalence is driven by heart failure medications, other cardiac medications or non-cardiac medications related to other comorbidity. A recent commentary by Roa et al. [38] has questioned the validity of the polypharmacy definition in heart failure, eluding to the fact that polypharmacy is in fact often seen as a negative, but can confer multiple therapeutic options and that a multidisciplinary approach should be taken to maximise the benefits of guideline-directed medical therapy and minimise adverse events, concluding that polypharmacy should be tailored to the individual. Very little data was presented on the classes of medications that contributed to polypharmacy, with only 9 studies [14, 18, 21, 27, 28, 30–33] displaying data on the proportion of patients using various therapeutic classes or individual agents. Given this, it is not possible to distinguish between 'appropriate polypharmacy' and 'inappropriate polypharmacy'. Measures of the prescription of multiple heart failure medications in combination, such as triple therapy of ACEi/ARB/ARNI, beta-blocker and MRA, are often used as markers of success in national audits and large observational cohorts [39–42]. Therefore, whether an arbitrary cut-off of medication number, rather than medication appropriateness, is a suitable characteristic to research remains unclear.

The heart failure population is ageing due to better cardiology interventions, better comorbid treatments and generally trends in population-level life-expectancy; hence, patients have growing numbers of comorbidities, which can exacerbate the occurrence of polypharmacy [43, 44]. Multimorbidity is common in heart failure [45] and is known to have a detrimental association with outcomes [46]. Increasing frailty in patients is negatively associated with quality of life and outcomes [47, 48]. Polypharmacy, multimorbidity and frailty are however closely linked [49] and therefore likely describe different sides of the same phenomena. To better understand the prognostic importance of polypharmacy, further focused research is need to unpick which has greatest predictive value for negative outcomes.

Comorbid medications are known to have the potential to both cause and exacerbate heart failure [50]. Polypharmacy, as shown in the study by Verdiani et al. [27], comes with an added level of therapeutic complexity due to the changes associated with advancing age and altered pharmacokinetics and pharmacodynamics and the increased risk of adverse drug reactions with polypharmacy regimens. This can often lead to a prescribing cascade of inappropriate polypharmacy whereby there is the addition of another medication to solve a medicine-related issue instead of withdrawal of the causative drug. Medication regimens of high complexity have been associated with non-adherence, poor quality of life, increased readmission to hospitals and adverse drug reactions (20, 51). Cobretti et al. [20] showed the average medication count to be 13.3 with 72% of the study populations taking eleven or more medications a day, 28% taking more than sixteen medications [34], well beyond most definitions for hyperpolypharmacy [12, 52].

The European Society of Cardiology guidelines for heart failure recommend that clinicians should aim to reduce polypharmacy where possible, including the complexity of regimens, and consider stopping medication without effect on prognosis, symptom relief or quality of life [8]. Deprescribing is a commonly promoted concept in older patients in order to reduce potential of adverse drug reactions and improve adherence to treatments [53]. Deprescribing has been associated with lower mortality in older person nursing departments and in institutional settings has been associated with reduced hospitalisation and maintenance of quality of life [51]. However, the commonly used Beers criteria [54] and STOPP/START describing tools [55] contain recommendations around the deprescribing of medications with key prognostic or symptomatic importance in heart failure. These tools have not been studied in a heart failure population and should only be used within the confines of an adequately designed study to assess their effectiveness and safety.

The studies in this review highlight that polypharmacy has the potential to create problems such as issues with adherence [20, 22, 26], drug-drug interactions [15] and adverse drug reactions [15, 20]. Such findings are consistent with the existing wider literature; non-adherence has long been known to be associated in-part with overall number of medications in heart failure [56], drug-to-drug interactions in comorbid heart failure patients are known to be plentiful [50], and adverse drug reactions are common in trials and real-life cohorts [57, 58].

As heart failure patients travel along the complex disease trajectory with worsening symptoms, deteriorating heart function and frequent hospital admissions, more pharmacological options become available, in addition to already prescribed medication in-line with evidence-based prescribing algorithms, resulting in medications accumulating in number and complexity along the way. As shown in the findings of this review, little is known about how polypharmacy trends change over time in patients throughout this journey. Heart failure has a mortality rate, which is higher than most cancers [59] and in the later stages of the disease when the focus shifts to palliative management and end-of-life care, more work is needed to understand whether these complex medication regimens should be rationalised and reviewed for appropriateness.

Studies included in this systematic review showed clear heterogeneity in terms of sample size, study population, type

of heart failure and polypharmacy measures, which make the findings difficult to interpret. What is clear is that regardless of definition, the prevalence of polypharmacy is high, especially in older patients. Future studies need to include all medication types, classes and dosage ranges and better define the type, aetiology and severity of heart failure; the presence of key comorbidities of interest; interactions between measures of multimorbidity, frailty and polypharmacy; drivers of polypharmacy (whether 'appropriate' vs 'inappropriate'); patterns and trends in polypharmacy over the different stages of the heart failure journey and the impact and consequence of polypharmacy on both hard outcomes and patient-reported outcome measures.

Strengths and limitations

This review was the first review aimed at addressing this topic and involved comprehensive searching five large databases using established methods and was prospectively registered with prospero and report in standardised way. Despite this, there were a number of limitations. Firstly, only studies in English language were included and reporting varied in quality. Polypharmacy prevalence was not the primary outcome measure in many of the studies resulting in a lack of in-depth information relating to it, the data presented in this review is based on original published data for each study rather than individual requested patient data where HF polypharmacy was not the main aim. It was often not clear if all medications were included, such as over-the-counter therapy, acute therapies (e.g. antibiotics) and non-oral medications (e.g. inhaled or topical therapies).

Conclusion

Polypharmacy is highly prevalent in the heart failure population. A unified definition was not found although polypharmacy is defined as greater than 5 medications in the majority of the studies. There is a need for an agreed definition of polypharmacy internationally which can then be quantified in various cohorts. Whether an arbitrary cut-off of medication number is a suitable definition, rather than medication appropriateness, remains unclear. Any future agreed definition needs to be better underpinned by further studies to understand the relationship of polypharmacy with specific types of heart failure, related comorbidities, other confounding factors and the impact on patient outcomes including HF-specific outcomes. As the evidence base for heart failure treatments grows, the resultant prescribing cascade to improve heart failure outcomes and symptoms will likely increase polypharmacy in the years ahead. This combined with advancing age and increasing levels of multimorbidity may put patients at further risk of polypharmacy and the associated negative effects.

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Author contribution JB: lead author, study design, search strategy, main reviewer of search results, main data extraction, main CASP analysis, and manuscript composition. MH: study design, lead for search strategy, pilot searches, pilot data extraction and manuscript composition and review. AH: third reviewer of search results and manuscript composition and review. AK: study design, search strategy and manuscript composition and review. PF: study concept and design, senior supervisor, search strategy, second screening of search results, data extraction validation, second CASP analysis, and manuscript composition and review.

Data availability Searches are available on request.

Declarations

Competing interests The authors declare no competing interests.

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