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RESEARCH ARTICLE

Global patterns of polypharmacy after acute heart failure hospitalization: Prevalence and outcomes from the REPORT-HF registry

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Aims Polypharmacy, defined as the concurrent use of ≥5 medications, is prevalent among older adults with heart failure (HF). While guideline-directed HF medications provide therapeutic benefits, non-HF polypharmacy, particularly involving inappropriate medications, may lead to adverse outcomes. The international REgistry to assess medical Practice with lOngitudinal obseRvation for Treatment of Heart Failure (REPORT-HF), the largest available global acute HF registry, was used to examine the prevalence, clinical correlates, and 1-year outcome associations of non-HF polypharmacy.

Methods and results Medication counts were classified as no polypharmacy (<5), polypharmacy (5–9), and hyper-polypharmacy (≥10). Potentially harmful medications were identified using the 2016 American Heart Association scientific statement. Multivariable regression models examined correlates of polypharmacy and 1-year mortality. Among 18 030 patients (66 ± 14 years, 39% women), 39% had polypharmacy and 9% had hyper-polypharmacy (63% and 25%, respectively, if including HF medications). Non-HF polypharmacy was more common in older white patients from high-income countries, with preserved ejection fraction and high comorbidity burden. Patients with greater non-HF medication use were less likely to receive guideline-directed HF medications

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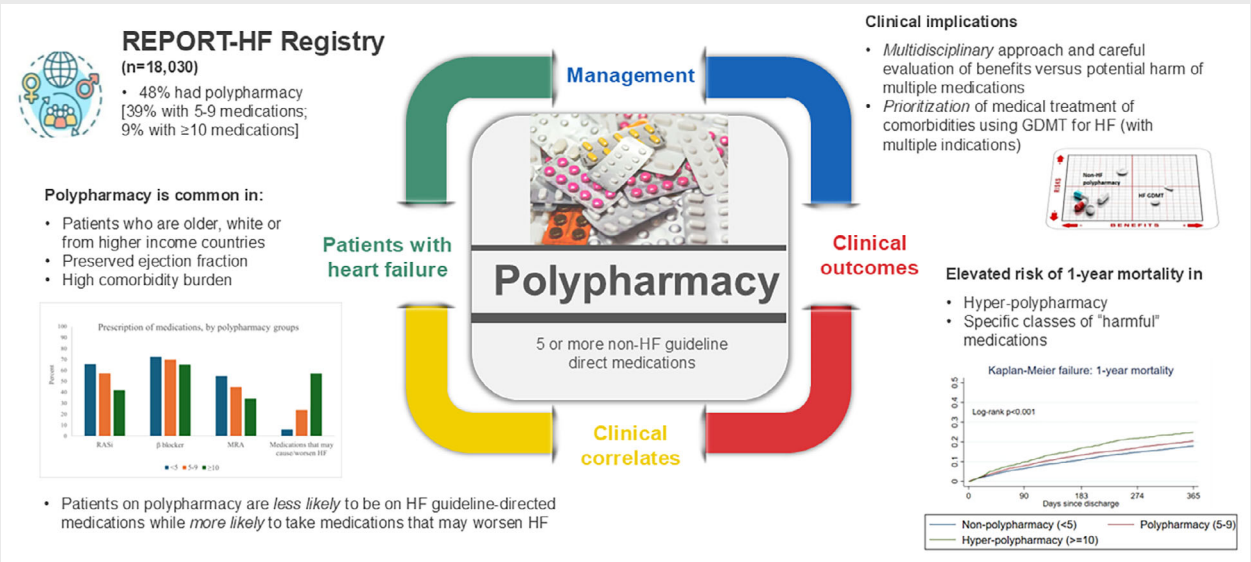
and more likely to take medications that can worsen HF. Crude hazard ratios (HRs) for 1-year mortality were 1.16 (95% confidence interval [CI] 1.08–1.25) for polypharmacy and 1.46 (95% CI 1.31–1.63) for hyper-polypharmacy versus no polypharmacy. After adjustment, hyper-polypharmacy remained associated with increased mortality (HR 1.16, 95% CI 1.01–1.33).

Conclusions Non-HF polypharmacy in HF is common worldwide, particularly in high-income regions. Its association with reduced use of guideline-directed HF medications and higher usage of medications causing or worsening HF, as well as elevated 1-year mortality, underscores the importance of addressing polypharmacy in HF.
Clinical Trial Registration: ClinicalTrials.gov NCT02595814.

Graphical Abstract



Global patterns of polypharmacy after acute heart failure hospitalization. GDMT, guideline-directed medical therapy; HF, heart failure.

Keywords Polypharmacy • Heart failure • Mortality • Hospitalization • Harmful medications

Introduction

Polypharmacy, defined as the simultaneous use of ≥5 medications,[1,2] is common in patients with heart failure (HF)[1,3] often due to the need to manage comorbidities other than HF, and is associated with adverse outcomes.[4–6] In recent years, polypharmacy has become an emerging aspect of HF care, especially in the more frail and elderly patients, complicating management due to its tolerability and potential drug–drug interactions.[7] The prevalence of polypharmacy varies across HF phenotypes. In patients with HF and preserved ejection fraction (HFpEF) from the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial, 92.5% were taking ≥5 medications (including HF drugs).[3] In the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial, 47% of patients with HF and reduced ejection fraction (HFrEF) were prescribed ≥5 medications.[8]

Given the robust evidence that HF guideline-directed medical therapies (GDMT) improve symptoms, reduce hospitalizations and mortality, even in elderly patients and regardless of ejection fraction, polypharmacy is often clinically justified in patients with HF.[9,10] This creates an inherent challenge: balancing the well-established benefits of optimized HF treatment against the potential harms of polypharmacy. Distinguishing appropriate (i.e. GDMT) from inappropriate polypharmacy in HF has been recognized as critically important.[4] Inappropriate polypharmacy is associated with potential harm, leading to under-prescription of GDMT, reduced medication adherence, adverse events, and

poorer outcomes.[4,5,8,11] In 2017, the World Health Organization emphasized polypharmacy as an action target to address unsafe medication practices leading to preventable harm.[12]

Global real-world data can inform strategies to optimize pharmacotherapy to improve the quality and safety of prescribing among patients with HF. Accordingly, we used the international REgistry to assess medical Practice with lOngitudinal obseRvation for Treatment of Heart Failure (REPORT-HF), the largest available global acute HF registry, to examine the prevalence, clinical correlates, and outcome associations of polypharmacy.

Methods

Study design, study population and setting

REPORT-HF is a global, prospective, and observational study designed to characterize global differences in clinical presentations, treatment, and patient trajectories longitudinally during and following an index hospitalization for HF. The study design, methods and outcomes of the REPORT-HF registry have been reported previously.[13,14] Patients with a primary diagnosis of acute HF (as diagnosed by the clinician investigator) were prospectively enrolled in 358 centres from 44 countries across six continents between July 2014 and March 2017. Details of the inclusion and exclusion criteria have been described elsewhere.[13,14] REPORT-HF identified all patients at admission with a primary acute HF diagnosis and excluded those enrolled in a concomitant clinical trial. Ethics approvals were obtained from each participating cente's local institutional review committee, and all participants provided written informed consent. This study conforms to the ethical guidelines in the Declaration of Helsinki and is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.

Data collection and definitions

Using uniform case report forms at all sites, investigators recorded data on demographics, clinical signs and symptoms on physical examination, New York Heart Association (NYHA) functional status, clinical chemistry, medical history, prior cardiac interventions, and medication history at admission and/or discharge. Comorbidities were determined based on medical history; anaemia was defined based on sex-specific haemoglobin levels. HFrEF was defined as left ventricular ejection fraction (LVEF) <40%, HF with mildly reduced ejection fraction (HFmrEF) as LVEF 40–49% and HFpEF as LVEF ≥50%.

Countries were stratified into subgroups based on the national income categorized by the World Bank classification into lower-middle-income countries (Lower), upper-middle income (Middle) and high-income (High) countries.[14,15]

Definition of polypharmacy and harmful medications

To distinguish GDMT for HF (the term 'GDMT' is exclusively for HF only) from other medications used in the management of comorbidities, we defined polypharmacy as the use of ≥5 medications, excluding HF medications (angiotensin-converting enzyme inhibitors [ACEi]/angiotensin receptor blockers [ARB], beta-blockers, mineralocorticoid receptor antagonists [MRA], and diuretics for fluid retention). We further categorized the number of remaining medications as <5 (non-polypharmacy), 5–9 (polypharmacy) and ≥10 (hyper-polypharmacy) to investigate a graded effect of polypharmacy on outcomes. Digoxin was included in the count for non-GDMT. Angiotensin receptor–neprilysin inhibitor (ARNI) and sodium–glucose co-transporter 2 (SGLT2) inhibitors were not examined as the REPORT-HF registry pre-dated the commercialization of these medications. Medication classes that can cause or worsen HF were identified based on an American Heart Association (AHA) scientific statement.[16] Only those with a level of evidence (LOE) A or B were included. Several therapeutic groups in the AHA scientific statement had similarly been highlighted in the 2021 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF[10] and the clinical consensus statement of the Heart Failure Association.[7]

Medications and dosages at discharge were collected from medical records at or around the time of discharge during the index hospitalization. Fractionated dose of the HF medications (ACEi/ARB/ARNI, beta-blockers and MRA) were calculated based on recommended target doses according to the ESC and AHA guidelines. Additional checks for total medication count were performed during analysis to account for duplicated or missing records. When no medications were recorded at discharge for the patient, we assumed these data were missing since it is unlikely a patient is not on any medication.

Outcomes

The primary outcome was 1-year all-cause mortality post-discharge from the index hospitalization. Mortality was prospectively captured during the follow-up from death records and phone follow-up visits. Patients were considered lost to follow-up if no vital status could be obtained.

Statistical analyses

Patients were stratified according to three polypharmacy subgroups: <5, 5–9 and ≥10 medications. Standard descriptive statistics, including mean ± standard deviation and median plus 25th–75th percentiles or numbers and percentages, were used to describe patient demographics and characteristics, clinical signs and symptoms, medical history/comorbidities, laboratory values, medications, and device therapy, as appropriate for the type and distribution of the data variable. Differences between the subgroups were tested using ANOVA, the Kruskal–Wallis test (for continuous skewed variables), and the χ^2 test (for categorical variables). The associations of polypharmacy and harmful medication with 1-year all-cause mortality were examined using a Cox proportional hazards model. Models were adjusted for age, sex, region, income class, length of stay, HF diagnosis, LVEF, peripheral oedema, NYHA class, systolic blood pressure, diabetes, chronic kidney disease (CKD), anaemia, coronary artery disease (CAD), valvular heart disease, use of ACEi/ARB, beta-blockers and MRA. Cox proportional hazards assumption was checked for all parameters using the proportionality test in Stata. Confounders were chosen based on clinical relevance and prior literature.[17] Additionally, we adjusted for the total number of drugs, excluding HF medications, in the models for harmful medications. Patients lost to follow-up were excluded from outcomes analysis, and only those with complete data on the variables listed above were included in the multivariable analyses. Sensitivity analyses were performed for polypharmacy including HF drugs. All analyses were two-tailed, and $p < 0.05$ was considered statistically significant. Analyses were performed in Stata v16 (StataCorp., College Station, TX, USA).

The funder of the REPORT-HF registry had no role in the study design, data collection, data analysis, data interpretation, or report writing.

Results

Baseline characteristics

Among 18 030 patients (mean age 66 ± 14 years, 39% women), the median number of medications was 7 (6–9) and 4 (3–7) at discharge, including and excluding HF medications, respectively. In total, 6991 (39%) and 1601 (9%) patients were prescribed with polypharmacy (5–9 medications other than HF medications) and hyper-polypharmacy (≥10 medications other than HF medications), respectively. The proportion of patients on ≥5 medications ranged from 40% in lower-middle and upper-middle-income to 58% in high-income countries.

Table 1 shows that patients prescribed more medications were older, more often white, residents of North America, Western Europe, or regions of higher national income and had more comorbidities, such as hypertension, CAD, diabetes, anaemia, CKD, asthma, peripheral arterial disease and stroke. Furthermore, these patients were more likely to have HFpEF than HFrEF or HFmrEF, have a higher NYHA class, and had worse renal function (estimated glomerular filtration rate) than patients without polypharmacy.

Polypharmacy (≥5 non-HF drugs) and hyper-polypharmacy (≥10 non-HF medications) were consistently associated with older age and increased comorbidity burden (*Table 2*, online supplementary *Table Appendix S1*). Notably, among those with hyper-polypharmacy, patients from North America and South East Asia regions had the highest (six–seven-fold) adjusted odds versus those from Western Europe of hyper-polypharmacy (online supplementary *Table Appendix S1*). Patients from South East Asia were however significantly younger with lower comorbidity burden (mean number of comorbidities 2.4 ± 1.4) than those from North America (4.3 ± 2.1).

Polypharmacy and medication prescription

With increasing polypharmacy, the number of patients being on HF guideline-directed drugs (ACEi/ARB, beta-blockers and MRA) declined ($p < 0.05$) (*Table 1*, *Figure 1*). This association persisted after correcting for confounders, including age, sex, and comorbidities. A small but significant reduction was observed for doses of beta-blockers prescribed with increasing medications (*Table 1*).

Medications that can cause or worsen HF were prescribed in 17.4% ($n = 3130$) of patients. *Figure 1* shows that medicines that may cause or worsen HF were prescribed in 57% of patients with hyper-polypharmacy, 24% of patients with polypharmacy and 6% without polypharmacy. When investigating subclasses of medications that might cause or worsen HF, pulmonary-related, anti-diabetic, anti-hypertensive, neurological, and psychiatric medications (including anti-depressants) were most commonly prescribed. These sub-classes were all more commonly prescribed in patients with polypharmacy than in those without polypharmacy.

Association of polypharmacy with 1-year all-cause mortality

After 1-year follow-up, there were 3451 (19.6%) deaths and 467 (2.6%) patients were lost to follow-up. Polypharmacy and hyper-polypharmacy were associated with higher risk of death (hazard ratio [HR] 1.16, 95% confidence interval [CI] 1.08–1.25, and HR 1.46, 95% CI 1.31–1.63, respectively) compared to no polypharmacy (both $p < 0.001$) (*Figure 2*). In multivariable analysis, only hyper-polypharmacy was associated with a higher risk (HR 1.16, 95% CI 1.01–1.33) (*Table 3*) of 1-year all-cause mortality. This association was consistent regardless of age, sex or LVEF phenotype ($p_{interaction}$ for all > 0.05). Hyper-polypharmacy remained associated with a higher risk of 1-year mortality (HR 1.17; 95% CI 1.01–1.35) after correcting for harmful medications.

When investigating the association of harmful medications with 1-year mortality, neurological and psychiatric medications were associated with worse 1-year mortality (adjusted HR 1.23, 95% CI 1.02–1.48) (*Table 3*). Separately, antidepressants (in particular, citalopram) also showed a trend with worse 1-year mortality (adjusted HR 1.31, 95% CI 0.99–1.73), regardless of HF phenotype ($p_{interaction} > 0.05$).

Sensitivity analyses

Sensitivity analyses, including HF medications, were repeated for outcomes and descriptives (online supplementary *Tables S2* and *S3*). Results remained comparable with those reported previously. Notably, hyper-polypharmacy was not associated with 1-year mortality when corrected for guideline-directed HF medications.

When examining cardiovascular death as an outcome, in unadjusted competing risk (non- cardiovascular and unknown deaths) analysis, non-HF polypharmacy (subdistribution HR 1.02, 95% CI 0.93–1.11) and hyper-polypharmacy (subdistribution HR 1.03, 95% CI 0.88–1.20) were not associated with 1-year cardiovascular mortality.

Discussion

Our study had three major findings: (i) polypharmacy was common, especially in high-income countries; (ii) patients with polypharmacy were less likely on HF GDMT but more likely on medication that may cause or worsen HF, independent of patients' comorbidity burden; and (iii) polypharmacy was associated with worse clinical outcomes, independent of medication that may cause or worsen HF (Graphical Abstract). This study is unique in that it differentiates between appropriate polypharmacy for HF and non-GDMT (including harmful medications), as evidence-based medications for HF improve life expectancy and/or re-hospitalization for HF. These results highlight a critical unmet need to frequently review medication lists to ensure all medications are clinically indicated and demonstrate the value of managing patients with HF in multidisciplinary care teams, with the inclusion of mental health professionals and primary care physicians who have an overview of all the medications prescribed. The findings also confirm the challenges and clinical dilemma inherent in caring for and managing older patients

Table 1 Baseline characteristics of patients by polypharmacy subgroups, excluding heart failure drugs

Characteristic	Number of drugs, excluding HF drugs			*p*-value
	<5	5–9	≥10	
n	9438	6991	1601	
Socio-demographic characteristics				
Age, years	66 (55–76)	69 (59–78)	69 (61–78)	<0.001
Men	5782 (61)	4357 (62)	919 (57)	0.001
Region				<0.001
Central and South America	1597 (17)	832 (12)	72 (4)	
Eastern Europe	1871 (20)	851 (12)	35 (2)	
Eastern Mediterranean region and Africa	1394 (15)	689 (10)	78 (5)	
North America	348 (4)	632 (9)	583 (36)	
South East Asia	869 (9)	1102 (16)	314 (20)	
Western Europe	1471 (16)	1643 (24)	371 (23)	
Western Pacific	1888 (20)	1242 (18)	148 (9)	
Regional income				<0.001
Lower middle income	1345 (14)	1363 (19)	301 (19)	
Upper middle income	4942 (52)	2351 (34)	186 (12)	
High income	3151 (33)	3277 (47)	1114 (70)	
HF diagnosis and severity				
Time since HF diagnosis, years	3 (1–6)	3 (1–7)	3 (1–7)	<0.001
NYHA class at discharge				<0.001
I	1244 (13)	688 (10)	87 (5)	
II	3430 (36)	2080 (30)	233 (15)	
III	1754 (19)	1050 (15)	169 (11)	
IV	350 (4)	206 (3)	59 (4)	
Missing/unknown	2660 (28)	2967 (42)	1053 (66)	
LVEF, %	37 (25–52)	37 (26–53)	40 (26–55)	<0.001
LVEF group				<0.001
<40%	4576 (48)	3356 (48)	708 (44)	
≥40% and <50%	1436 (15)	1102 (16)	260 (16)	
≥50%	2573 (27)	1948 (28)	522 (33)	
Unknown	853 (9)	585 (8)	111 (7)	
DCHF vs. new-onset HF	4281 (45)	2904 (42)	534 (33)	<0.001
Clinical examination				
Systolic blood pressure, mmHg	117 (105–129)	120 (110–130)	120 (110–135)	<0.001
Diastolic blood pressure, mmHg	70 (61–80)	70 (60–80)	70 (60–78)	<0.001
eGFR, ml/min/1.73 m^2	59.2 (42.7–77.1)	51.2 (35.3–70.3)	43.1 (29.0–62.2)	<0.001
Medical history				
Hypertension	5489 (58)	4827 (69)	1190 (74)	<0.001
Atrial fibrillation/flutter	2839 (30)	2225 (32)	557 (35)	<0.001
CAD	3664 (39)	4026 (58)	991 (62)	<0.001
COPD/asthma	969 (10)	1131 (16)	484 (30)	<0.001
Anaemia	3467 (37)	3764 (54)	1188 (74)	<0.001
Valvular heart disease	1955 (21)	1299 (19)	281 (18)	<0.001
PAD	327 (3)	399 (6)	143 (9)	<0.001
Stroke/TIA	493 (5)	575 (8)	180 (11)	<0.001
Thyroid dysfunction	596 (6)	695 (10)	265 (17)	<0.001
Sleep apnoea	163 (2)	273 (4)	200 (12)	<0.001
Liver disease	263 (3)	205 (3)	71 (4)	0.002
Diabetes	2519 (27)	3350 (48)	1019 (64)	<0.001
Chronic kidney disease	1371 (15)	1671 (24)	583 (36)	<0.001
Cancer	350 (4)	456 (7)	155 (10)	<0.001
Neurological or psychiatric condition	431 (5)	504 (7)	236 (15)	<0.001
No. of comorbidities[a]	3 (1–4)	4 (2–5)	5 (3–6)	<0.001

Table 1 (Continued)

Characteristic	Number of drugs, excluding HF drugs			*p*-value
	<5	5–9	≥10	
Device therapy				
Pacemaker	432 (5)	388 (6)	150 (9)	<0.001
CRT-pacemaker	51 (1)	53 (1)	16 (1)	0.054
CRT-defibrillator	148 (2)	173 (2)	70 (4)	<0.001
ICD	274 (3)	392 (6)	175 (11)	<0.001
HF GDMT and harmful medications				
ACEi/ARB	6196 (66)	4011 (57)	668 (42)	<0.001
ACEi/ARB dose	0.33 (0.25–0.57)	0.33 (0.25–0.63)	0.33 (0.17–0.63)	0.26
Beta-blocker	6835 (72)	4871 (70)	1045 (65)	<0.001
Beta-blocker dose	0.25 (0.13–0.50)	0.25 (0.24–0.50)	0.25 (0.13–0.50)	<0.001
MRA	5177 (55)	3129 (45)	546 (34)	<0.001
MRA dose	0.33 (0.33–0.53)	0.33 (0.33–0.50)	0.33 (0.33–0.67)	0.6
Harmful drugs (LOE A or B)	557 (6)	1657 (24)	916 (57)	<0.001

Values given as median (interquartile range), or *n* (%).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DCHF, decompensated chronic heart failure; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LOE, level of evidence; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PAD, peripheral arterial disease; TIA, transient ischaemic attack.
[a]Cardiovascular comorbidities included hypertension, CAD, atrial fibrillation or atrial flutter, and valvular heart disease. Non-cardiovascular comorbidities included anaemia, diabetes, renal failure, COPD or asthma, sleep apnoea, PAD, liver disease, cancer, thyroid dysfunction, stroke or TIA, other neurological conditions, and psychiatric conditions.

with HF, who commonly have advanced disease conditions, with complex drug regimens.

Our study found that 48% of patients were discharged from the hospital with polypharmacy, varying from 40% in lower-middle/middle-income countries to 58% in high-income countries. When HF medications were included, polypharmacy increased substantially to 87% overall. Though high, this rate is lower than previous studies,[3,5,18] including TOPCAT Americas, where 92.5% of HFpEF patients had polypharmacy,[3] and the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, which reported 95% of patients on polypharmacy, including HF medications.[18] Our findings likely differ from previous studies because REPORT-HF participants were younger, had acute HF, more often had HFrEF, and had fewer comorbidities.[19,20] Importantly, our research expands on earlier US-based findings[3,5,18] by including data from 44 countries across different economic levels. Notably, we saw that patients from South East Asia were significantly younger with lower comorbidity burden compared to those from North America, alluding to the more fragmented care in South East Asia than North America or Western Europe.

Patients on polypharmacy were less likely to be on HF GDMT[8,11] but more likely on medications that might cause or worsen HF.[4,5] These results are consistent with previous findings from the REGARDS study.[11] In a separate survey among primary care providers, polypharmacy was identified as a significant barrier to initiating and titrating beta-blockers.[21] Similarly, we observed a significant dose reduction for beta-blockers among patients with polypharmacy in our study. These findings also align with a study from the GUIDE-IT trial.[8] Our study extends previous findings by demonstrating that these results are consistent outside the United States. Polypharmacy is intricately linked to medication non-adherence; increase in number of medications inherently increases the risk of medication non-adherence.[22] Therefore, striking a balance between optimization of GDMT for HF and avoidance of inappropriate polypharmacy is crucial in the contemporary care of patients with HF.[7]

Prior research on medications that may cause or worsen HF in patients with existing HF has been limited, with only one study conducted in the United States using the REGARDS registry.[23] In that study, over half of the patients were on medications that may cause or worsen HF. Our study builds upon these findings in two ways. First, we demonstrate a novel association between polypharmacy and an increased likelihood of receiving medications that may worsen HF. Second, we show that potentially harmful medication prescribing patterns are also prevalent in lower-income countries.

Hyper-polypharmacy was independently associated with a higher risk of 1-year all-cause mortality. Previous studies reported that polypharmacy is associated with worse clinical outcomes.[3,4,18,24] Importantly, our study is the first to show the association of subclasses of medications that may cause or worsen HF with a higher mortality risk. We found that neurological and psychiatric drugs were associated with a higher 1-year mortality risk. Many of these drugs, such as citalopram, are associated with delayed QT syndrome and an increased risk of torsades de pointes. The risk of torsades de pointes is increased in patients with HF, which might explain our findings.[25] Additionally, tricyclic antidepressants had been reported to cause orthostatic hypotension, slowed cardiac conduction, increased heart rate and decreased heart rate variability, among other related adverse effects.[26,27] Notably, the association of hyper-polypharmacy with 1-year mortality disappeared after adjustment for HF GDMT. This might suggest that

Table 2 Correlates of polypharmacy (≥5 non-heart failure drugs)

Characteristic	Crude OR (95% CI)	*p*-value	Adjusted[a] OR (95% CI)	*p*-value
Age, per 10 years	1.20 (1.17–1.23)	<0.001	1.08 (1.05–1.11)	<0.001
Men	1.01 (0.95–1.07)	0.844	1.08 (1.01–1.16)	0.028
Region				
Central and South America	0.41 (0.37–0.46)	<0.001	0.70 (0.62–0.80)	<0.001
Eastern Europe	0.35 (0.31–0.38)	<0.001	0.45 (0.39–0.52)	<0.001
Eastern Mediterranean region and Africa	0.40 (0.36–0.45)	<0.001	0.65 (0.56–0.75)	<0.001
North America	2.55 (2.22–2.92)	<0.001	2.47 (2.12–2.87)	<0.001
South East Asia	1.19 (1.07–1.33)	0.002	2.34 (1.97–2.77)	<0.001
Western Europe	1.0 (Ref)		1.0 (Ref)	
Western Pacific	0.54 (0.49–0.59)	<0.001	1.00 (0.88–1.13)	0.981
Regional income				
Lower middle income	0.89 (0.82–0.97)	0.006	1.05 (0.91–1.21)	0.523
Upper middle income	0.37 (0.34–0.39)	<0.001	0.66 (0.59–0.73)	<0.001
High income	1.0 (Ref)		1.0 (Ref)	
NYHA class at discharge				
I	1.0 (Ref)			
II	1.08 (0.98–1.20)	0.136		
III	1.12 (0.99–1.25)	0.064		
IV	1.22 (1.01–1.46)	0.037		
Missing/Unknown	2.43 (2.19–2.69)	<0.001		
LVEF group				
<40%	1.0 (Ref)		1.0 (Ref)	
≥40% and <50%	1.07 (0.98–1.16)	0.131	0.94 (0.86–1.04)	0.225
≥50%	1.08 (1.01–1.16)	0.028	0.95 (0.88–1.03)	0.25
DCHF vs. new-onset HF	0.80 (0.76–0.85)	<0.001		
Systolic blood pressure, mmHg	1.01 (1.01–1.01)	<0.001		
Diastolic blood pressure, mmHg	1.00 (0.99–1.00)	0.002		
eGFR, ml/min/1.73 m^2	0.99 (0.99–0.99)	<0.001		
Hypertension	1.68 (1.58–1.79)	<0.001		
Atrial fibrillation/flutter	1.11 (1.04–1.19)	0.001		
CAD	2.21 (2.08–2.35)	<0.001		
COPD/asthma	2.02 (1.86–2.20)	<0.001		
Anaemia	2.34 (2.21–2.49)	<0.001		
Valvular heart disease	0.86 (0.80–0.93)	<0.001		
PAD	1.88 (1.63–2.16)	<0.001		
Stroke/TIA	1.75 (1.55–1.97)	<0.001		
Thyroid dysfunction	1.87 (1.68–2.08)	<0.001		
Sleep apnoea	3.31 (2.77–3.97)	<0.001		
Liver disease	1.16 (0.97–1.37)	0.095		
Diabetes	2.84 (2.67–3.02)	<0.001		
Chronic kidney disease	2.09 (1.94–2.25)	<0.001		
No. of comorbidities	1.48 (1.45–1.50)	<0.001	1.53 (1.50–1.57)	<0.001

CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DCHF, decompensated chronic heart failure; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OR, odds ratio; PAD, peripheral arterial disease; TIA, transient ischaemic attack.

[a]Adjusted for age, sex, region, regional income, LVEF and number of comorbidities.

the principal harm of polypharmacy could lie in its interference with optimal HF therapy, rather than in direct adverse effects. Evidence-based HF therapies are associated with improvement in symptoms and quality of life; this aspect of care remains critically important even when life prolongation is not possible.

Collectively, our findings highlight the issue of 'therapeutic competition' in clinical practice, where one medication used to treat one condition is harmful to another, particularly common in the context of elderly patients with multimorbidity. Given the risks of adverse events associated with polypharmacy, it underscores stringent assessment of the trade-off between benefits versus harms of medications prescribed, not only for the underlying condition of interest but also other co-existing conditions.[7] The recent clinical consensus statement of the Heart Failure Association of the ESC[7] also highlighted the importance of prioritizing medical treatment of comorbidities using GDMT for HF (with multiple indications)

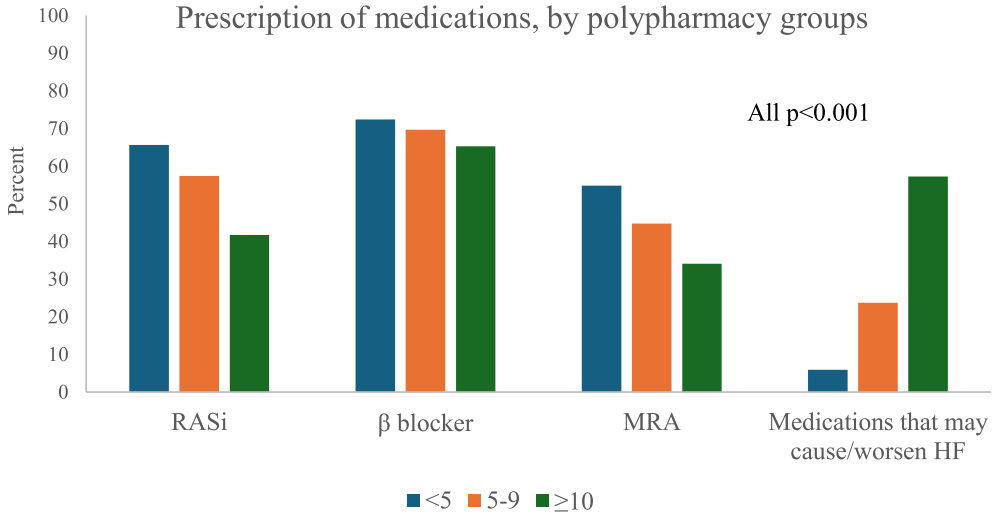


Figure 1 Prescription of medications (heart failure [HF] guideline-directed medical therapies and drugs that may cause or worsen HF). MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor.

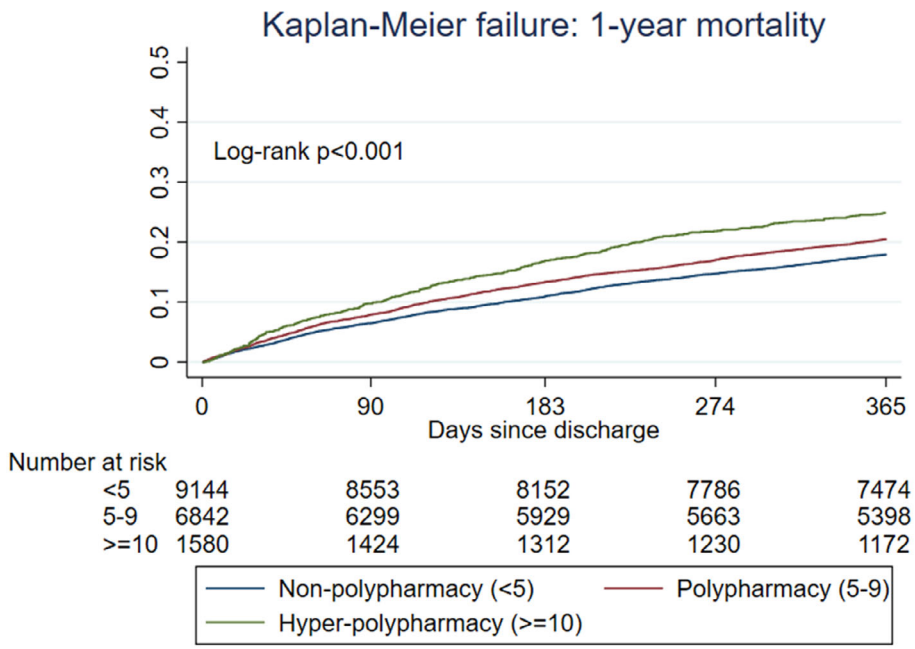


Figure 2 Kaplan–Meier survival curves: association of polypharmacy categories with 1-year mortality.

to reduce the pill-load. Such an opportunity could be applied to the management of hypertension, CAD, diabetes and even CKD which have the highest odds of polypharmacy (*Table 2*). Additionally, where possible, it is important to consider de-prescribing or reducing the dose of certain medications or substituting therapeutic agents with broader indications but a better side-effect profile.[28] De-prescribing older medications with relatively new multi-modal medications with broader indications, might be one approach going forward. For example, SGLT2 inhibitors[29] have been approved for multiple indications (as one of the four pillars of GDMT for HF, type 2 diabetes and CKD) owing to their ability to lower the risk of cardiovascular death, HF hospitalizations and retard CKD progression, making them an attractive treatment option. ARNI (also indicated for HF) modulate multiple cardiac and non-cardiac peptides, extending beyond pre-existing antihypertensive agents.[30]

Recently, there is a paradigm shift from whether polypharmacy is 'good' or 'bad' to appropriateness of polypharmacy.[4] Even the

Table 3 Associations of polypharmacy (excluding heart failure drugs) and harmful medications with 1-year mortality

Variable	1-year all-cause mortality							
	No. at risk	Deaths (%)	Crude HR (95% CI)	*p*-value	Adjusted[a] HR (95% CI)	*p*-value	Adjusted[b] HR (95% CI)	*p*-value
Polypharmacy, excluding HF drugs								
<5	9144	1637 (17.9)	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
≥5	8422	1791 (21.3)	1.22 (1.14–1.30)	<0.001	1.04 (0.96–1.13)	0.321	1.02 (0.94–1.10)	0.714
Polypharmacy, excluding HF drugs								
<5	9144	1637 (17.9)	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
5–9	6842	1399 (20.5)	1.16 (1.08–1.25)	<0.001	1.03 (0.94–1.12)	0.543	1.00 (0.92–1.09)	0.915
≥10	1580	392 (24.8)	1.46 (1.31–1.63)	<0.001	1.16 (1.01–1.33)	0.041	1.09 (0.95–1.26)	0.214
Harmful LOE A/B drug								
No	14 565	2871 (19.7)	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	3055	580 (19.0)	0.96 (0.88–1.05)	0.390	0.99 (0.89–1.10)	0.870	0.97 (0.87–1.08)	0.609
LOE A drug								
No	17 021	3329 (19.6)	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	599	122 (20.4)	1.05 (0.87–1.26)	0.589	1.13 (0.93–1.37)	0.227	1.11 (0.91–1.34)	0.312
LOE B drug								
No	14 818	2918 (19.7)	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	2802	533 (19.0)	0.97 (0.88–1.06)	0.455	0.98 (0.88–1.10)	0.722	0.96 (0.86–1.08)	0.516
Specific therapeutic classes of 'harmful meds'								
DM medications								
No	16 857	3324 (19.7)	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	763	127 (16.6)	0.83 (0.70–1.00)	0.045	0.87 (0.72–1.06)	0.180	0.88 (0.72–1.07)	0.199
Antihypertensive medications								
No	16 902	3341 (19.8)	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	718	110 (15.3)	0.76 (0.62–0.91)	0.004	0.80 (0.64–0.99)	0.040	0.75 (0.60–0.93)	0.010
Neurological and psychiatric medications								
No	16 974	3302 (19.5)	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	646	149 (23.1)	1.23 (1.04–1.45)	0.015	1.22 (1.02–1.47)	0.034	1.23 (1.02–1.48)	0.028
Antidepressants (citalopram)								
No	17 372	3394 (19.5)	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	248	57 (23.0)	1.22 (0.94–1.59)	0.131	1.29 (0.98–1.71)	0.073	1.31 (0.99–1.73)	0.060

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; LOE, level of evidence; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure

[a]Adjusted for age, sex, SBP, HF history, NYHA class at discharge, peripheral oedema, diabetes, CAD, anaemia, CKD, valvular heart disease, LVEF group, region, income, length of stay, and number of drugs (excluding HF).

[b]Adjusted for age, sex, SBP, HF history, NYHA class at discharge, peripheral oedema, diabetes, CAD, anemia, CKD, valvular heart disease, LVEF group, region, income, length of stay, use of ACEi/ARB, beta-blocker, MRA and number of drugs (excluding HF).

essence of de-prescribing is to ensure that appropriate drug treatments are used, not so much to reduce the count of medications.[7] In targeting polypharmacy, life-prolonging medications should be prioritized during the process of medication review or reconciliation; appropriateness of non-HF treatment medications and de-prescribing (if needed) for the management of comorbidities should be critically reassessed.[7] Furthermore, outpatient cardiology follow-up had been shown to improve outcomes in HF.[31,32] Nevertheless, an integrated and multidisciplinary approach (with the inclusion of mental health professionals) to managing multimorbidity and polypharmacy in HF, focusing on the appropriateness of medications prescribed, with the goal of optimizing medical therapy in HF, should be considered in the development of future clinical practice guidelines. An individualized medication plan consolidated by healthcare professionals (with involvement of the patient), and checked for medical, pharmaceutical or adherence problems and only listing prognostic or quality of life improving medication would be useful.

Of note, the use of over-the-counter medications and health supplements, which adds to the medication burden, is common among individuals with cardiovascular disease.[33,34] Such non-prescription products could have adverse drug–drug interactions with other medications, posing challenges to patient safety and health outcomes[35]; yet these are often not disclosed to healthcare providers. The disclosure of these non-prescription products is crucial; hence HF professionals should be mindful to consistently query its use.

Limitations

There were limitations to our investigation. We cannot discriminate whether excess mortality is due to the increased mortality risk associated with the comorbidities for which specific drugs are given, or with the drugs themselves or with both. Conversely, non-GDMT drugs might also have a favourable impact on the HF course or symptoms. The streamlined case report forms did not describe the indications, duration of therapy, or all medications prescribed. Persistence and adherence data of medications were therefore lacking. Use of over-the-counter drugs, such as health supplements was not collected. Polypharmacy is a key risk factor for drug–drug interactions among older patients; however, this aspect has not been examined in our study. Newer therapeutic agents, such as SGLT2 inhibitors and ARNI, were not investigated; contemporary data across multiple countries using newer

agents would offer more scope. Serial serum creatinine measurements were not available to assess the association of polypharmacy with renal function longitudinally. Only a small proportion (5%) of patients were on device therapy, which could have been an enabler for GDMT. Some comorbidities (e.g. mental health) were not collected, and the prognostic impact of the comorbidities themselves cannot be discriminated from the effect of the drugs applied for specific conditions. Finally, as an observational study, causality cannot be established.

Conclusions

Polypharmacy was common in this global cohort of patients with acute HF, with marked geographical variation across regions. Older age and multimorbidity were essential correlates of polypharmacy. Patients on polypharmacy were less likely to be on HF GDMT and more likely to be on medications that can cause or worsen HF. Importantly, polypharmacy, especially hyper-polypharmacy, conferred a higher risk of poorer outcomes. The high risk of adverse events from polypharmacy emphasizes the need for careful evaluation of medication benefits versus potential harms, not only for HF but also for coexisting conditions. In developing future clinical practice guidelines, an integrated approach to managing multimorbidity and polypharmacy should be considered.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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References

1. Beezer J, Al Hatrushi M, Husband A, Kurdi A, Forsyth P. Polypharmacy definition and prevalence in heart failure: A systematic review. *Heart Fail Rev* 2022;**27**:465–492. https://doi.org/10.1007/s10741-021-10135-4
2. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr* 2017;**17**:230. https://doi.org/10.1186/s12877-017-0621-2
3. Minamisawa M, Claggett B, Suzuki K, Hegde SM, Shah AM, Desai AS, *et al.* Association of hyper-polypharmacy with clinical outcomes in heart failure with preserved ejection fraction. *Circ Heart Fail* 2021;**14**:e008293. https://doi.org/10.1161/CIRCHEARTFAILURE.120.008293
4. Sukumar S, Orkaby AR, Schwartz JB, Marcum Z, Januzzi JL, Vaduganathan M, *et al.* Polypharmacy in older heart failure patients: A multidisciplinary approach. *Curr Heart Fail Rep* 2022;**19**:290–302. https://doi.org/10.1007/s11897-022-00559-w
5. Wu Y, Zhu W, He X, Xue R, Liang W, Wei F, *et al.* Influence of polypharmacy on patients with heart failure with preserved ejection fraction: A retrospective analysis on adverse outcomes in the TOPCAT trial. *Br J Gen Pract* 2021;**71**:e62–e70. https://doi.org/10.3399/bjgp21X714245
6. Tromp J, Tay WT, Ouwerkerk W, Teng TK, Yap J, MacDonald MR, *et al.* Multimorbidity in patients with heart failure from 11 Asian regions: A prospective cohort study using the ASIAN-HF registry. *PLoS Med* 2018;**15**:e1002541. https://doi.org/10.1371/journal.pmed.1002541
7. Stolfo D, Iacoviello M, Chioncel O, Anker MS, Bayes-Genis A, Braunschweig F, *et al.* How to handle polypharmacy in heart failure. A clinical consensus statement of the Heart Failure Association of the ESC. *Eur J Heart Fail* 2025;**27**:747–759. https://doi.org/10.1002/ejhf.3642
8. Khan MS, Singh S, Segar MW, Usman MS, Keshvani N, Ambrosy AP, *et al.* Polypharmacy and optimization of guideline-directed medical therapy in heart failure: The GUIDE-IT trial. *JACC Heart Fail* 2023;**11**:1507–1517. https://doi.org/10.1016/j.jchf.2023.03.007
9. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:1757–1780. https://doi.org/10.1016/j.jacc.2021.12.011
10. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
11. Onyebeke C, Zhang D, Musse M, Unlu O, Nahid M, Ambrosy AP, *et al.* Polypharmacy and guideline-directed medical therapy initiation among adults hospitalized with heart failure. *JACC Adv* 2024;**3**:101126. https://doi.org/10.1016/j.jacadv.2024.101126

12. Donaldson LJ, Kelley ET, Dhingra-Kumar N, Kieny MP, Sheikh A. Medication without harm: WHO's third global patient safety challenge. *Lancet* 2017;**389**:1680–1681. https://doi.org/10.1016/S0140-6736(17)31047-4
13. Filippatos G, Khan SS, Ambrosy AP, Cleland JG, Collins SP, Lam CS, *et al.* International REgistry to assess medical practice with lOngitudinal obseRvation for Treatment of Heart Failure (REPORT-HF): Rationale for and design of a global registry. *Eur J Heart Fail* 2015;**17**:527–533. https://doi.org/10.1002/ejhf.262
14. Tromp J, Bamadhaj S, Cleland JGF, Angermann CE, Dahlstrom U, Ouwerkerk W, *et al.* Post-discharge prognosis of patients admitted to hospital for heart failure by world region, and national level of income and income disparity (REPORT-HF): A cohort study. *Lancet Glob Health* 2020;**8**:e411–e422. https://doi.org/10.1016/S2214-109X(20)30004-8
15. Tromp J, Ouwerkerk W, Cleland JGF, Angermann CE, Dahlstrom U, Tiew-Hwa Teng K, *et al.* Global differences in burden and treatment of ischemic heart disease in acute heart failure: REPORT-HF. *JACC Heart Fail* 2021;**9**:349–359. https://doi.org/10.1016/j.jchf.2020.12.015
16. Page RL, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, *et al.* Drugs that may cause or exacerbate heart failure: A scientific statement from the American Heart Association. *Circulation* 2016;**134**:e32–e69. https://doi.org/10.1161/CIR.0000000000000426
17. Tromp J, Ouwerkerk W, Teng TK, Cleland JGF, Bamadhaj S, Angermann CE, *et al.* Global disparities in prescription of guideline-recommended drugs for heart failure with reduced ejection fraction. *Eur Heart J* 2022;**43**:2224–2234. https://doi.org/10.1093/eurheartj/ehac103
18. Unlu O, Levitan EB, Reshetnyak E, Kneifati-Hayek J, Diaz I, Archambault A, *et al.* Polypharmacy in older adults hospitalized for heart failure. *Circ Heart Fail* 2020;**13**:e006977. https://doi.org/10.1161/CIRCHEARTFAILURE.120.006977
19. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 2009;**48**:143–157. https://doi.org/10.2165/00003088-200948030-00001
20. Ueno K, Sato H. Sex-related differences in pharmacokinetics and pharmacodynamics of anti-hypertensive drugs. *Hypertens Res* 2012;**35**:245–250. https://doi.org/10.1038/hr.2011.189
21. Levitan EB, Van Dyke MK, Loop MS, O'Beirne R, Safford MM. Barriers to beta-blocker use and up-titration among patients with heart failure with reduced ejection fraction. *Cardiovasc Drugs Ther* 2017;**31**:559–564. https://doi.org/10.1007/s10557-017-6764-8
22. Lavrador M, Cabral A, Castel-Branco M, Figueiredo I, Fernandez-Llimos F. Polypharmacy and medication adherence. In: Oliveira PJ, Malva JO, eds. *Aging: From Fundamental Biology to Societal Impact*. Academic Press: London; 2023. p435–453.
23. Goyal P, Kneifati-Hayek J, Archambault A, Mehta K, Levitan EB, Chen L, *et al.* Prescribing patterns of heart failure-exacerbating medications following a heart failure hospitalization. *JACC Heart Fail* 2020;**8**:25–34. https://doi.org/10.1016/j.jchf.2019.08.007
24. Ozasa N, Kato T, Morimoto T, Yaku H, Yamamoto E, Inuzuka Y, *et al.* Polypharmacy and clinical outcomes in hospitalized patients with acute decompensated heart failure. *J Cardiovasc Nurs* 2023;**38**:33–43. https://doi.org/10.1097/JCN.0000000000000885
25. Wolbrette DL. Drugs that cause torsades de pointes and increase the risk of sudden cardiac death. *Curr Cardiol Rep* 2004;**6**:379–384. https://doi.org/10.1007/s11886-004-0041-8
26. Behlke LM, Lenze EJ, Carney RM. The cardiovascular effects of newer antidepressants in older adults and those with or at high risk for cardiovascular diseases. *CNS Drugs* 2020;**34**:1133–1147. https://doi.org/10.1007/s40263-020-00763-z
27. Woron J, Siwek M, Gorostowicz A. Adverse effects of interactions between antidepressants and medications used in treatment of cardiovascular disorders. *Psychiatr Pol* 2019;**53**:977–995. https://doi.org/10.12740/PP/OnlineFirst/96286
28. Bricca A, Smith SM, Skou ST. Management of multimorbidity. *J Multimorb Comorb* 2023;**13**:26335565231156693. https://doi.org/10.1177/26335565231156693
29. Peikert A, Goyal P, Vaduganathan M, Claggett BL, Kulac IJ, Miao ZM, *et al.* Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction according to polypharmacy status. *JACC Heart Fail* 2023;**11**:1380–1393. https://doi.org/10.1016/j.jchf.2023.05.014
30. Yamamoto K, Rakugi H. Angiotensin receptor-neprilysin inhibitors: Comprehensive review and implications in hypertension treatment. *Hypertens Res* 2021;**44**:1239–1250. https://doi.org/10.1038/s41440-021-00706-1
31. Baudry G, Pereira O, Roubille F, Villaceque M, Damy T, Duarte K, *et al.* Cardiologist follow-up and improved outcomes of heart failure: A French nationwide cohort. *Eur Heart J* 2025;**46**:3050–3065. https://doi.org/10.1093/eurheartj/ehaf218
32. Tay WT, Teng TK, Ouwerkerk W, Angermann CE, Dickstein K, Cleland JGF, *et al.* Quality of care delivery in patients with acute heart failure: Insights from the international REPORT-HF registry. *EClinicalMedicine* 2025;**80**:103031. https://doi.org/10.1016/j.eclinm.2024.103031
33. Ewen S, Baumgarten T, Rettig-Ewen V, Mahfoud F, Griese-Mammen N, Schulz M, *et al.* Analyses of drugs stored at home by elderly patients with chronic heart failure. *Clin Res Cardiol* 2015;**104**:320–327. https://doi.org/10.1007/s00392-014-0783-2
34. Mattila M, Boehm L, Burke S, Kashyap A, Holschbach L, Miller T, *et al.* Nonprescription medication use in patients with heart failure: Assessment methods, utilization patterns, and discrepancies with medical records. *J Card Fail* 2013;**19**:811–815. https://doi.org/10.1016/j.cardfail.2013.10.009
35. Kim J, Kincaid JWR, Rao AS, Lie W, Fuh L, Landman AB, *et al.* Risk stratification of potential drug interactions involving common over-the-counter medications and herbal supplements by a large language model. *J Am Pharm Assoc (2003)* 2025;**65**:102304. https://doi.org/10.1016/j.japh.2024.102304