Potentially Inappropriate Prescriptions in Heart Failure with Reduced Ejection Fraction (PIP-HFrEF)

Position statement on HFrEF specific inappropriate prescribing

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Table of Contents

List of Abbreviations

ACE: angiotensin-converting enzyme

ARB: angiotensin type II receptor blocker

ATC WHO, Anatomical Therapeutic Chemical Classification System

AV: atrioventricular

Ca^{2+}: calcium ion

CAD: coronary artery disease

CAM: complementary and alternative medicine

CAP: community acquired pneumonia

CCB: calcium channel blocker

CI: confidence interval

COPD: chronic obstructive pulmonary disease

COX-2: cyclo-oxygenase type 2

CYP: cytochrome P450

DPP-4I: dipeptidyl peptidase-4 inhibitors

ECG: electrocardiogram

EF: ejection fraction

EMA: European Medicines Agency

ESC: European Society of Cardiology

FDA: Food and Drug Administration

GDMT: guideline-directed medical therapy

HF: Heart Failure

HFrEF: heart failure with reduced ejection fraction

HR: hazard ratio

IV: intravenous

LV: left ventricular

LVEF: left ventricular ejection fraction

LVSD: left ventricular systolic dysfunction

MACE: major adverse cardiovascular events

MI: myocardial infarction

Na^{+}: sodium ion

NDP-CCB: non-dihydropyridine calcium channel blockers

NSAID: non-steroidal anti-inflammatory drug

NYHA: New York Heart Association

O_2: oxygen

OR: odds ratio

OTC: over the counter

PDE: phosphodiesterase

PIP-HFrEF: potentially inappropriate prescribing in heart failure with reduced ejection fraction

RR: relative risk

SDC: serum digoxin concentrations

SGLT2: Sodium-glucose co-transporter-2

SSRI: selective serotonin reuptake inhibitor

$t_{1/2}$: half-life

T2DM: type 2 diabetes Mellitus

UK: The United Kingdom

US: The United States

What does the statement add?

- First comprehensive evidence-based prescribing review tool for HFrEF in presence of comorbidities.
- Easy application in routine clinical practice for better management of HF therapeutic conflicts.
- Provided with efficacy data and the association of clinical outcomes.
- Included several important instances of inappropriate prescribing.

Abstract

Heart failure (HF) is a chronic debilitating and potentially life-threatening condition. Heart Failure patients are usually at high risk of polypharmacy and consequently, potentially inappropriate prescribing leading to poor clinical outcomes. Based on the published literature, a comprehensive HF-specific prescribing review tool is compiled to avoid medications that may cause HF or harm HF patients and to optimize the prescribing practice of HF guideline-directed medical therapies. Recommendations are made in line with the last versions of ESC guidelines, ESC position papers, scientific evidence, and experts' opinions.

Keywords: Heart Failure; Pharmacotherapy; Inappropriate prescribing; Therapeutic conflicts; reduced ejection fraction; comorbidities

Introduction

Heart Failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and clinical signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by structural and/or functional cardiac abnormalities, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[1,2] Chronic HF constitutes a major public health problem and remains the leading discharge diagnosis among patients ≥ 65 years of age.[3,4]

According to ESC 2016 Guidelines for The Diagnosis and Treatment of Acute and Chronic Heart Failure, the goals of therapy in patients with HF with reduced ejection fraction (HFrEF) aim to improve their clinical status, functional capacity, and quality of life, prevent hospital admission, and reduce mortality.[1] The fact that several medications for HFrEF have shown detrimental effects on long-term outcomes, despite showing beneficial effects on shorter-term surrogate markers, has led regulatory bodies and clinical practice guidelines to seek mortality/morbidity data for approving and recommending certain therapeutic interventions for HFrEF management.[5-8] However, it is now recognized that preventing HF hospitalization and improving functional capacity are important benefits to be considered if a mortality excess can be ruled out.[9]

HF patients are particularly vulnerable because of a broad-spectrum of comorbidity burden, disability, and frequent physician visits.[2-4] In HFrEF patients, this comorbidity burden is progressively increasing, with over 40% of patients having five or more chronic conditions.[10-12] Consequently, this increase is significantly associated with an increase in all-cause hospitalizations; interestingly, more than half of all hospitalizations of patients with HF are related to non-cardiovascular diseases.[10-12] Comorbidities associated with increased mortality

include diabetes mellitus, chronic kidney disease, cerebrovascular disease, depression, functional impairment, sleep-disordered breathing, and cognitive impairment.[2,13]

Because the high number of non-cardiovascular comorbidities in HF patients, the required number of medications prescribed also increases, leading to complex dosing regimens and potential therapeutic conflicts. Hence, more medications may reflect guideline-concordant care, but may also simultaneously increase the risk for harmful drug interactions and adverse drug events.[14-17] Additionally, patients with chronic illnesses like HF also consume a progressively increasing the number of over-the-counter (OTC) medications (e.g. non-steroidal anti-inflammatory drugs, NSAIDs) or complementary and alternative medications (CAM) which may exert direct adverse cardiac effects and/or interact with the guideline-directed medical therapies (GDMT).[18]

Polypharmacy commonly defined as the use of at least 5 medications (not including OTCs, dietary supplements, or herbal medicines) is particularly prevalent in older adults with HF.[10,19,20] The current ESC HF guidelines basically recommend up to seven drugs for the treatment of HF.[1] But because HF patients frequently have multiple comorbidities, polypharmacy is higher in patients with left ventricular systolic dysfunction (LVSD) compared with controls, with the biggest difference found for ≥11 repeat prescriptions (OR 4.81; 95%CI 4.60-5.04).[12,15] However, differences in polypharmacy are attenuated when accounting for the number of morbidities, indicating that much of the additional prescribing was accounted for by multimorbidity rather than LVSD *per se*. Apart from an increased risk of possible adverse drug effects, polypharmacy reduces adherence and increases the probability of under-prescription and under-dosing of the full list of GDMT.[15,21-24]

Furthermore, several drugs may cause a sizeable decrease in cardiac contractility and/or exert unfavourable hemodynamic effects by increasing cardiac preload and/or afterload, and consequently, they may induce HF in patients without concurrent cardiovascular diseases or may act as a precipitating factor for HF worsening in patients with previously compensated chronic HF.[25,26] The risk of an adverse drug-drug interaction climbs from 13% for patients taking at least two prescription medications to 82% with seven or more medications.[15,27] Many of these drug-disease and drug-drug interactions are deemed harmful to HF patients. Well described examples of this harmful interaction are NSAIDs, non-dihydropyridine calcium channel blockers (CCB), and thiazolidinediones.[1,6]

The ESC 2016 guidelines of HF briefly address the point of inappropriate prescribing in the form of potential drug interactions that may result in lower efficacy, poorer safety, the occurrence of unfavourable side effects, or worsening HF.[1] The ESC guidelines mention NSAIDs, thiazolidinediones, non-dihydropyridine CCBs, and beta-2 agonists as therapeutic conflicts with GDMT in HF patients.[1] Furthermore, the literature about disease-specific potentially inappropriate prescribing towards HF patients in routine clinical practice is still scarce.[14,15,17,23,28-33]

Additionally, older adults are the biggest consumers of prescription and OTC medications and dietary supplements and are most vulnerable to medication adverse events and for harm from serious drug-drug interactions.[20]

In order to minimize risks, clinicians must avoid prescribing inappropriate medications, adjust medication choices and dosages to reach an optimal risk-benefit balance, and remain ever vigilant to the potential for medications to cause or worsen HF.[23,24]

Therefore, this evidence-based statement aims to provide practical considerations for reducing inappropriate prescribing and improving medication safety in HF prescribing practice. The present statement summarizes and evaluates available evidence on the issue of potentially inappropriate prescribing in HFrEF (PIP-HFrEF) to assist healthcare providers to make safe decisions in their routine clinical practice by optimizing the output of GDMT prescription for an individual patient with a given condition, taking into account the impact on HF clinical outcomes, as well as the risk-benefit ratio of particular diagnostic or therapeutic means. However, the final decisions concerning an individual patient must be made by the responsible health professionals in consultation with the patient and caregiver as appropriate.

Data sources

A detailed review of case reports, case series, retrospective, and prospective interventional and non-interventional clinical studies, narrative and systematic reviews, and meta-analysis as well as the FDA Drug Safety Communications, the European Medicines Agency (EMA) reports and the medication leaflets and summary of drug product characteristics. A literature search was performed using the keywords: *inappropriate, cardiotoxic, myocardial toxicity, negative inotropic, harmful, drugs, medications, drug-induced* meshed with the keyword *heart failure* in PubMed, and Ovid. The literature search was not limited by date or language. Scientific evidence was searched in detail to back up the medications identified from medication leaflets, summaries of drug product characteristics, EMA reports, and FDA Drug Safety Communications.

Potentially Inappropriate Prescribing in HFrEF (PIP-HFrEF)

Medications are deemed to be appropriately prescribed when they have a clear evidence-based indication, are cost-effective, safe, and are well tolerated.[31] Potentially inappropriate prescribing is defined as *"the practice of administering medications in a manner that poses more risk than benefit, particularly where safer alternatives exist".*[30,31,34] Inappropriate prescribing introduces the risk of an adverse drug event which has the potential to outweigh the medication's clinical benefit, mainly when a safer or more effective alternative treatment option is available.[28] PIP-HFrEF refers to medications or medication classes that are not recommended in HFrEF patients based on reported evidence due to a harmful drug-disease/drug interaction.[1,6]

Medication effect

The statement included certain medications that are used in HFrEF patient populations and caused myocardial toxicity, negative inotropic, lusitropic, or chronotropic effects, or exacerbated underlying LVSD, leading to HF precipitation, exacerbation, or mortality as well as the medications that developed de-novo HF in patients of non-HF history, Figure 1. The

reported medication's effect was addressed via drug-disease and drug-drug interactions. Medications showing cardiac adverse events that are not direct or specific to HF prognosis or HF GDMT are not included. Also, the anti-neoplastic medications are not included herein due to the higher priority of cancers management in routine clinical practice. However, their cardiotoxicities have been clearly addressed in another ESC statement.[35] The level of evidence and the effect magnitude of PIP-HFrEF are described in Table 1.

Clinical Presentation and Differential Diagnosis

The clinical presentation of patients with PIP-HFrEF is not different from that from other causes. Symptoms may occur gradually following the initiation of a PIP-HFrEF item. The differential diagnosis of PIPHFrEF-induced versus other clinical causes of HF or its exacerbation may be challenging to distinguish from other common precipitants, such as sodium and fluid excess, myocardial ischemia, poor adherence to HF GDMT, uncontrolled hypertension, tachyarrhythmias, serious systemic infections, renal dysfunction, anaemia, thyrotoxicosis, ethanol ingestion, pulmonary embolism, and respiratory insufficiency. However, a temporal sequence of PIP-HFrEF items administration or PIP-HFrEF dose increase with the onset of emerging HF manifestations heightens the suspicion of a PIP-HFrEF-induced cause.[25,36,37]

Risk Factors

Patients can be predisposed to PIP-HFrEF by several modifiable and non-modifiable risk factors, Figure 2.

List of PIP-HFrEF items

Table 2 mentions the specific PIP-HFrEF agents while Table 3 mentions the PIPHFrEF classes deemed harmful in HFrEF.

I) Antiarrhythmic PIP-HFrEF items

Class I

Most antiarrhythmic drugs (mainly class I drugs, i.e. Na^+ channel blockers, like disopyramide and flecainide) decrease cardiac contractility and may induce or worsen congestive HF.[38-40] This negative inotropic effect can be related to the blockade of the L-type Ca^{2+} current and to the fact that inhibition of Na^+ channels by antiarrhythmic drugs alters the Na^+-Ca^{2+} exchange, leading to a decrease in the Ca^{2+} content in the sarcoplasmic reticulum and the Ca^{2+} entry through the exchanger.[40]

Class II

Because of their negative chronotropic and inotropic properties, they can induce or exacerbate HFrEF. However, four beta-blockers that are licensed for use in HF patients: bisoprolol, carvedilol, metoprolol, and nebivolol, should be initiated in clinically stable patients at a low dose and gradually uptitrated to the maximum tolerated dose according to the patient's status.[1] In patients admitted due to acute HF, β-blockers should be cautiously initiated in the hospital, once the patient is hemodynamically stabilized and decongested.[1]

In a Danish nationwide cohort study, prescription of carvedilol for HF patients with concurrent chronic obstructive pulmonary disease (COPD) increased HF hospitalization (1.61; 95%CI 1.52–1.70) compared with metoprolol, bisoprolol, and nebivolol use.[41] It was hypothesized that the antagonistic effect of carvedilol on prejunctional and postjunctional β2 receptors played an important role in the observed increase in risk.

β-blockers used to treat glaucoma, mainly timolol, are generally safe, but can be absorbed systemically to induce bronchospasm, heart block, and decompensate HFrEF, or cause adverse central nervous system effects in some patients.[25,26,42,43] Thus, caution should be taken when

ophthalmic β-blockers are administered to elderly patients or patients with contraindications to systemic β-blockers on long-term or chronic use.

The co-administration of β-blockers with other antiarrhythmic agents increases the risk of hypotension, bradycardia, and AV block and can precipitate HF. Its coadministration with digoxin increases the risk of bradycardia and AV block. Thus, close ECG and blood pressure monitoring is highly recommended. Intravenous β-blockers should not be given to patients treated with verapamil, whereas verapamil may increase the plasma concentrations of metoprolol and propranolol.

Class III

Class III antiarrhythmics are considered to lack the negative inotropic properties of Class I, probably because they prolong the plateau phase of the action potential and the time for Ca^{2+} entry through L-type calcium channels.[44]

However, sotalol, a non-selective β1-blocker that inhibits the rapid component of the delayed rectifier K^+ current (I_{Kr}), can significantly depress cardiac contractility and exacerbate HF in some patients and should be used cautiously in patients with LVSD. In patients treated for cardiac arrhythmias with sotalol, HF was reported in 3.3% in patients without previous HF history and in 10% of patients with a previous history of congestive HF or structural heart disease.[45]

During chronic oral therapy, class III antiarrhythmic drugs exert minimal effects on left ventricular ejection fraction (LVEF) in patients with normal, or near-normal LV function and some drugs (amiodarone) may increase slightly the LVEF if their vasodilatory effect reduces LV afterload. However, antiarrhythmic drugs significantly reduce LVEF in patients with pre-existing LVSD or structural heart disease, or when they are administered as intravenous

formulation or in high doses.[39,46] Furthermore, antiarrhythmic drugs can counteract the positive inotropic effect of digoxin and exert additive effects on sino-atrial and AV nodal function. However, antiarrhythmic drugs may improve LVEF in patients with tachyarrhythmias because the increase in heart rate may have a deleterious effect on LV function.

Dronedarone is a non-iodinated benzofuran derivative with a structure and mechanism of action similar to that of amiodarone.[47-49] The ANDROMEDA trial examined the effect of dronedarone on death and hospitalization for HFrEF in patients hospitalized with new or worsening HF and who had had at least one episode of shortness of breath on minimal exertion or at rest or paroxysmal nocturnal dyspnoea within the month before admission. The trial was prematurely terminated because treatment with dronedarone was associated with increased early mortality as compared with placebo (8.1% vs 3.8%; P=0.03) which was predominantly related to worsening of HFrEF.[49]

The PALLAS trial studied the clinical benefit of Dronedarone on top of the study standard regimen in patients with permanent atrial fibrillation and additional risk factors such as patients with HF, coronary artery disease (CAD), or prior stroke, as well as patients ≥75 years with hypertension and diabetes.[47] This study was prematurely stopped due to the significant increase in HF rate (HR 2.49, 95%CI 1.66-3.74); stroke (HR 2.14, 0.92-4.96) and cardiovascular death (HR 2.53, 0.98-6.53). In this study, the use of digoxin was associated with an increased risk of arrhythmia or sudden death in dronedarone-treated patients, compared to placebo. Thus, the dose of digoxin should be halved, and digoxin plasma levels carefully monitored.

There have been spontaneously reported post-marketing events of new or worsening HFrEF during treatment with dronedarone. Thus, dronedarone should be avoided in patients in unstable

hemodynamic conditions, with a history of, or current HF or LVSD, and treatment should be discontinued if LVSD or HF develops.[40]

Dronedarone also increases the exposure of β-blockers metabolized by CYP 2D6 (metoprolol, propranolol) and the risk of bradycardia and AV block. Thus, β-blockers should be used with caution concomitantly with dronedarone. In patients already taking β-blockers, an ECG should be performed, and the beta-blocker dose should be adjusted if needed.

Diltiazem and verapamil increase dronedarone exposure, while dronedarone increases the exposure to diltiazem, nifedipine, and verapamil. The coadministration of these drugs should be initiated at low doses and their uptitration should be done only after a baseline ECG assessment and gradually.

Class IV

Calcium channel blockers are generally contraindicated in patients with HFrEF.[1,7,50] Calcium channel blockers inhibit Ca^{2+} entry through the voltage-gated L-type Ca^{2+} channels and produce bradycardia and slow AV nodal conduction and reduce cardiac contractility.

The MDPIT trial showed a significant bidirectional interaction between diltiazem and pulmonary congestion.[51-53] In post-infarction patients without pulmonary congestion, diltiazem reduced the number of cardiac events (HR 0.77; 95%CI 0.61-0.98), while in patients with pulmonary congestion, diltiazem increased number of cardiac events (HR 1.41; 1.01-1.96).[51,52] In a post-hoc analysis of this trial, found that patients with pulmonary congestion, anterolateral Q-wave infarction, or reduced EF at baseline (≤40%) were more likely to have congestive HF during follow-up than those without these markers of LVSD.[51] These findings suggested that non-dihydropyridine CCBs (diltiazem or verapamil) should be avoided in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.[1,53]

Diltiazem and verapamil also inhibit CYP3A4 enzymes increasing the exposure of drugs that are substrates of CYP3A4. Verapamil may increase the plasma concentrations of metoprolol and propranolol which may adversely lead to additive cardiovascular events (e.g. AV block, bradycardia, hypotension, HF).[54]

The cardio-depressant effects of CCBs can be unmasked in patients treated with β-adrenergic blockers or with LVSD or a previous myocardial infarction (MI), where they can deteriorate LV function and worsen HF.[55-57] A combination of CCBs, particularly non-dihydropyridine CCBs (diltiazem, verapamil), with β-blockers should be avoided in patients with LVSD or HF unless administered under close medical supervision. Intravenous β-blockers should not be given to patients treated with verapamil. In patients treated with β-blockers, the administration of diltiazem or verapamil produce additive reductions in heart rate, AV nodal conduction, and cardiac contractility and potentially serious cardio-depressant effects (bradycardia, AV block, and HF) may occur.[55-57] The risk is increased with high dosages, IV administration, LVSD, or AV conduction abnormalities. Therefore, this combination should be restricted to hospital practice, where the dose of each drug can be carefully titrated, and the patient closely supervised, and dose up-titration should be done only after ECG assessment. Beta-blocker ophthalmic solutions may also interact, as they are systemically absorbed and can produce clinically significant systemic effects even at low or undetectable plasma levels.

Coadministration of diltiazem or verapamil and antiarrhythmics may lead to additive cardio-depressant effects and should be avoided. Verapamil may decrease the clearance of flecainide and increases plasma quinidine levels. The combination of verapamil with inhaled anaesthetics may increase the risk of HF and should be avoided. Diltiazem and verapamil are not

recommended to reduce blood pressure in patients with HFrEF because of their potent negative inotropic action, increasing the risk of HF worsening and HF hospitalizations.

Dihydropyridine CCBs directly depress cardiac contractility and may have deleterious effects in patients with HF, although they can increase LVEF by the reflex activation of the sympathetic tone which counteracts their negative inotropic effect. There is only evidence that felodipine[58] and amlodipine[59] can be safely added in patients with HF on standard therapy with uncontrolled hypertension or angina.

Digoxin interactions

Digoxin has a narrow therapeutic index so minor changes and fluctuations in plasma concentration may readily lead to toxic or sub-therapeutic concentrations.[60,61] Digoxin plasma levels are increased by amiodarone, dronedarone, flecainide, propafenone, quinidine, and verapamil.

Dronedarone increases plasma digoxin concentrations and exerts a synergistic effect on heart rate and AV conduction. If digoxin treatment is continued, the dose of digoxin should be halved, and close monitoring of the ECG and digoxin plasma levels closely are recommended. Also, verapamil decreases the clearance and increases the plasma levels of digoxin; thus, plasma digoxin levels should be monitored, and the dose should be appropriately reduced to avoid digitalis toxicity.

II) Antifungal PIP-HFrEF items

Amphotericin B

Infusion-related reactions of Amphotericin-B include chest discomfort, dyspnoea, hypoxia, tachycardia, and hypotension.[62] These manifestations may resolve just upon discontinuation or the end of the infusion, although severe infusion-related reactions may require permanent

discontinuation of the medication. Caution must be taken when administering Amphotericin B to prevent overdose, which can result in potentially fatal cardiac or cardiorespiratory arrest if the dose prescribed exceeds 1.5 mg/kg/day.[63-66] Cases of new-onset dilated cardiomyopathy with subsequent HF have been reported; symptoms normalized within 6 months of discontinuation.[62,67,68] Amphotericin B produces hypokalaemia and may potentiate the effects of digoxin.[63-66]

Itraconazole

Itraconazole is an antifungal agent with negative inotropic effects[69] which has been associated with occasional reports of cardiotoxicity, including new-onset and worsening HF, peripheral oedema, and pulmonary oedema.[70-72] Heart failure was more frequently reported among spontaneous reports of 400 mg total daily dose than among those of lower total daily doses, suggesting that the risk of HF might increase with the total daily dose of itraconazole.[70-72] Thus, itraconazole should not be used in patients with LVSD or congestive HF or patients at risk of HF unless a strong benefit clearly outweighs the risk in absence of a safer alternative. The FDA recommends against the use of itraconazole in patients with evidence of LVSD such as congestive HF or a history of HF.

Itraconazole is a strong CYP3A4 inhibitor that increases the exposure of calcium channel blockers (CCBs: dihydropyridines, diltiazem, and verapamil) and statins (atorvastatin, lovastatin, simvastatin). Therefore, concurrent administration of itraconazole with these drugs should be carried out under close monitoring and their dosage should be reduced when coadministered with itraconazole. Also, the combination of itraconazole and eplerenone is contraindicated in HF patients.

III) Antihypertensive PIP-HFrEF items

ACE-inhibitor and ARB combination

Individually, these two pharmacological classes are deemed to be the most important guideline-directed medical therapies in HF management. However, several studies revealed that the combination of an ACE-inhibitor and an ARB (or renin inhibitor) increased the risk of hypotension, syncope, decreased renal function (including acute renal failure), and hyperkalaemia.[73-77]

In patients with MI complicated by HF and/or LVSD combining valsartan with captopril increased the rate of adverse events without improving survival.[77] Thus, in the ESC Guidelines, the addition of an ARB (or renin inhibitor) to the combination of an ACE-inhibitor and an MRA is not recommended in patients with HFrEF, because of the increased risk of renal dysfunction and hyperkalaemia**.**[1,78]

The combination of ACE-inhibitor/ARB should be restricted to symptomatic HFrEF patients receiving a beta-blocker who are unable to tolerate an MRA and must be used under strict supervision by the cardiologist. Also, it is important to take into account the possibility of the occurrence of first dose syncope with this combination.[1,78]

High Dosing and combination of loop diuretics

Loop diuretics are strongly recommended to reduce the signs and symptoms of congestion in HF patients,[1,7,8,50,79] but their effects on mortality and morbidity have not been studied in large randomized clinical trials and so prospective trials are.[80] Because each type of diuretics acts at a different site of the nephron, a combination of diuretics acting at a different site to produce a *sequential nephron blockade* allows us to obtain an additive diuretic effect in patients with severe HF or refractory oedema. This combination is preferred to higher doses or the combination of two loop diuretics. Nevertheless, the former requires careful monitoring of fluid

status and serum electrolyte levels to avoid dehydration, hypokalaemia, hyponatraemia, hypovolaemia, or renal dysfunction.[1,7,8,50]

Several studies have addressed the effect of co-administration of two loop diuretic agents in HFrEF.[81, 82] The results did not show any promising impact on mortality, hospitalization, or quality of life; however, this inappropriate duplication increased the rates of adverse drug reactions in HFrEF patients.[83-86]

In patients with advanced HF, there was an independent, dose-dependent association between loop diuretic use and impaired survival.[87] Higher loop diuretic dosages identify patients with HF at particularly high risk for mortality.[86] Among 15,141 patients with a median age of 86 years, long-term furosemide prescription rate increased with age, and this increase was associated with a decrease in recommended HF therapeutics (beta-blockers, ACE-inhibitors or ARBs).[85] In the EVEREST trial, higher short-term diuretic exposure during hospitalization for worsening HF was not an independent predictor of 30-day all-cause mortality and HF rehospitalization.[84] The lack of association between diuretic dose and mortality/HF re-hospitalizations is consistent with the findings of the DOSE trial, which reported no differences in patients' global assessment of symptoms or in the change in renal function when diuretic therapy was administered by bolus as compared with continuous infusion or at a high dose as compared with a low dose.[88]

Other antihypertensive agents

Doxazosin and prazosin inhibit postsynaptic α1-adrenergic receptors and produce arterial and venous vasodilation. In the ALLHAT trial, the doxazosin arm of the study was terminated prematurely because the risk of HF was doubled (2.04; 95%CI, 1.79–2.32) as compared with chlorthalidone.[89, 90] The increased risk of HF has been related to sodium and fluid retention, a smaller blood pressure reduction with doxazosin, and the unmasking of HF in patients with

LVSD rather than causing HF per *se* [91] In the VeHFT trial, treatment with prazosin, another α-blocker also showed no benefits in patients with HFrEF as compared with placebo, whereas cumulative mortality was lowered by 38% with combination therapy of isosorbide dinitrate and hydralazine.[92]

Minoxidil is an arterial vasodilator with little effect on veins. In 17 patients with chronic HF after 3 months of treatment, minoxidil significantly increased LVEF, but does not affect exercise performance or symptomatic status; however, increased the need for diuretics, angina, ventricular arrhythmias, worsening HF, and death versus placebo.[93] Therefore, minoxidil should not be used in HF patients.[94]

Moxonidine is a new-generation alpha-2/imidazoline receptor agonist antihypertensive drug licensed for the treatment of mild to moderate essential hypertension. However, in MOXCON trial, an early increase in the rates of mortality, HF hospitalization and major adverse cardiac events (MACE) was reported in the moxonidine arm of patients that led to premature termination of the trial because of safety concerns.[95] Thus, moxonidine should not be prescribed to HFrEF patients.[94]

IV) Anti-inflammatory and immunosuppressant PIP-HFrEF items

Corticosteroids

Glucocorticoid excess increases fluid retention, induces cardiovascular risk factors (obesity, insulin resistance, glucose intolerance, dyslipidaemia, and hypertension), accelerates the progression of atheromatous vascular disease, and increases the incidence of HF.[96]

In HF patients, higher serum levels of both cortisol were independent predictors of increased mortality risk (HR for highest versus lowest tertile of cortisol 2.72, 1.38-5.36).[97] Treatment with high-dose glucocorticoids seemed to be associated with an increased risk for cardiovascular

event[98] and was identified as a risk factor for HF (2.66, 2.46-2.87).[99] The use of glucocorticoids is associated with an increased risk of HF (OR 2.66, 2.46-2.87) in patients with rheumatoid arthritis and/or chronic obstructive pulmonary disease.[100] There was a relationship between daily dose and risk of HF among current users of oral glucocorticoids (OR 1.95, 1.72-2.21 for low dose (<7.5 mg prednisolone equivalent daily dose); OR 2.27, 2.00-2.59 for medium dose (7.5–20 mg prednisolone equivalent daily dose); and OR 3.69, 3.26-4.18 for high dose (>20 mg prednisolone equivalent daily dose).[99]

Mineralocorticoids (e.g., fludrocortisone) may antagonize the effects of mineralocorticoid receptor antagonists and in patients with Addison's disease mineralocorticoid overdose has been implicated in LVSD in Addison's disease.[68,69] The association of congestive HF with fludrocortisone therapy was reported in 7 of 22 adults with Addison's disease followed for over 30 years.[101]

Cyclosporine

Cases of HF and oedema adverse events have been reported from post-marketing surveys where the frequency of this adverse drug reaction is not known due to the lack of a real denominator.[102,103] Additionally, cyclosporin produces dyslipidaemia and hyperkalaemia, particularly in patients with renal dysfunction. Regular monitoring of blood pressure, lipids profile, and serum potassium levels are recommended when cyclosporin is co-administered with potassium-sparing drugs (e.g. potassium-sparing diuretics, ACE-inhibitors, ARBs) or potassium-containing medicinal products. Cyclosporin increases exposure to digoxin.

NSAIDs (including COX-2 inhibitors)

Nonsteroidal anti-inflammatory drugs are frequently prescribed in patients with HF.[104] NSAIDs increase renal sodium and water retention, may worsen kidney function, especially in patients with pre-existing renal impairment and antagonize the effects of ACE-inhibitors/ARBs,

diuretics, and possibly β-blockers in patients with HF.[105] Several studies found an association between traditional NSAIDs use and HF precipitation and/or worsening.[18,106-108] Initiation of NSAID therapy may double the risk of developing HFrEF in susceptible individuals.[104,109]

Patients with renal failure, diabetes, or hypertension when taking NSAIDs might be at a greater risk of developing HF than patients without those conditions.[110, 111] In the Rotterdam study, patients with prevalent HF who filled at least 1 NSAID prescription since diagnosis of HF had a 10-fold increased risk of a relapse (RR 9.9, 1.7–57.0).[112] The use of NSAIDs in elderly patients taking diuretics is associated with a 2-fold increased risk of hospitalization for HF compared with the use of diuretics only, especially in patients with an existing condition of HF.[113] The recent use of NSAIDs by elderly patients doubles the odds of HF hospitalization (OR 2.1, 1.2-3.3).[105] In another study, NSAIDs increased the risk of first hospital admission for HF (1.3, 1.1-1.6), but in patients with a prior clinical diagnosis of HF, the use of NSAIDs may lead to worsening of pre-existing HF that triggers their hospital admission (HR 8.6, 5.3-13.8) compared with patients who did not use NSAIDs and without a prior diagnosis of HF.[114] Among first-time cases with a history of heart disease, the use of non-aspirin NSAIDs in the week before admission was associated with an OR of 10.5 (2.5-44.9), compared with 1.6 (0.7-3.7) in those without such a history.[105] The odds of the first admission to a hospital with HF were positively related to the dose of NSAID consumed in the previous week and increased to a greater extent with long half-life than with short half-life drugs. Several studies compared the cardiovascular safety of traditional NSAIDs and COX2 inhibitors. The use of any NSAID (in the preceding 14 days) was associated with an increased risk of hospital admission for HF (OR 1.19; 1.17-1.22), compared with past use of any NSAIDs (>183 days in the past).[115] Risk of admission for HF increased for traditional NSAIDs (diclofenac, ibuprofen, indomethacin, ketorolac, naproxen, nimesulide, piroxicam) and COX-2 inhibitors (etoricoxib, rofecoxib) and

this effect was dose-dependent. There was no evidence that celecoxib increased the risk of admission for HF at commonly used doses.

In a Danish nationwide population of 36,354 ambulatory HF patients, treatment with NSAIDs, both selective COX-2 inhibitors and nonselective NSAIDs were associated with increased mortality and cardiovascular morbidity (hospitalization because of acute MI and HF), with a dose-dependent response.[18] Therefore, patients with HF should, if possible, avoid using any NSAIDs at any dosage for most NSAID agents and particularly, at high dosages for ibuprofen and naproxen.

In a Canadian retrospective population-based study, relative to non-NSAID users, patients on rofecoxib and non-selective NSAIDS had an increased risk of admission for congestive HF (OR 1.8, 95%CI 1.5-2.2, and 1.4, 1.0-1.9, respectively), but this was not shown for celecoxib.[116] Compared with celecoxib users, admission was significantly more likely in users of non-selective NSAIDs (1.4, 1.0-1.9) and rofecoxib (1.8, 1.4-2.4). The risk of admission for rofecoxib users was higher than that for non-selective NSAID users (1.5, 1.1-2.1). Of patients with no admission in the past 3 years, only rofecoxib users were at increased risk of subsequent admission relative to controls (1.8, 1.4-2.3). These findings suggest a higher risk of admission for HF in users of rofecoxib and non-selective NSAIDs, but not celecoxib, relative to non-NSAID controls. Similarly, the risk of death and recurrent HF exacerbation combined was higher in elderly patients prescribed NSAIDs or rofecoxib than in those prescribed celecoxib (HR 1.26, 1.00-1.57, and 1.27, 1.09-1.49, respectively). Celecoxib seems safer than rofecoxib and NSAIDs.[117] Nevertheless, celecoxib use for the prevention of colorectal adenomas was associated with a dose-related increase in the composite endpoint of death from cardiovascular causes, MI, stroke, or HF.

In the ESC guidelines, NSAIDs or COX-2 inhibitors are not recommended in HFrEF patients as they increase the risk of HF worsening and hospitalization.[1] Efforts should be made to promote the rational use of NSAIDs in the general population and they should be used with caution by patients at high risk of developing HF or with HF.[104] Pending comprehensive safety analyses, the use of NSAIDs in high-risk patients should be discouraged.

TNF-alpha inhibitors

Post-marketing reports of new-onset or worsening HF, with and without identifiable precipitating factors, even in patients without known pre-existing cardiovascular disease and under 50 years of age have been reported with TNF-α inhibitors.

In a retrospective cohort study of elderly patients with rheumatic arthritis and prior history of HF, TNF-α inhibitors use increases the risk of HF hospitalization (1.70, 95%CI 1.07-2.69) and death and death (HR 4.19, 1.48–11.89) compared with methotrexate use.[118] However, in a recent large meta-analysis of RCTs and extension studies of biologics (including anti-TNF biologics) for various indications, there was no increase in the risk of HF (OR 0.69, 0.18-2.69). [119] In the ATTACH trial higher rates of HF-related hospitalization or death were observed in patients with NHYA class III-IV HF receiving infliximab 10 mg/kg as compared with the 5-mg/kg dose (HR 2.84, 1.01-7.97).[120] Similarly, the combined risk of all-cause or HF hospitalization through 28 weeks increased in the patients randomized to 10 mg/kg infliximab (HR 2.84, 1.01-7.97).[121] The results of RENEWAL trial were sufficiently unfavourable as to rule out a clinically relevant benefit of etanercept on the rate of hospitalization due to chronic HF.[122]

The 2015 American College of Rheumatology treatment guidelines for rheumatoid arthritis recommended that TNF-α inhibitors should be used with caution in patients with mild HF (NYHA class I/II) if no other reasonable treatment options are available, but contraindicated their use in patients with moderate or severe HF.[123] Patients should be closely monitored, and

TNF-α inhibitors should be discontinued in patients who develop new or worsening symptoms of HF.

V) Central nervous system PIP-HFrEF items

Antiepileptics

Carbamazepine is a Na^+ channel blocker that binds preferentially to an inactive state of voltage-gated sodium channels and slows the rate of recovery from inactivation. It is used as an antiepileptic, mood stabilizer, and anti-neuropathic pain. Severe LVSD with a reduction in LVEF to less than 35% has been described in cases of overdose even in patients without preexisting cardiac disease.[124-126]

Pregabalin is an analogue of the neurotransmitter γ-aminobutyric acid[127] that binds to the α_2-δ auxiliary subunit of voltage-gated calcium channels in the central nervous system which exhibits analgesic, anticonvulsant, and anxiolytic properties.[127] There are post-marketing reports of congestive HF and LVSD in patients receiving pregabalin for neuropathic pain, particularly in elderly cardiovascular compromised patients.[128-130] Thus, pregabalin should be used with caution in these vulnerable patients. Although the mechanism of pregabalin-induced HF is uncertain, a calcium channel blockade has been suggested, which might explain why the clinical deterioration in HF status is seen particularly in patients with LVSD.[129] In controlled clinical trials, pregabalin use increases the incidence of peripheral oedema and weight gain, with cases reported in patients both with and without HF.[127-129,134]

Antiparkinsonian drugs

Some studies have suggested a potential risk of HF in patients with Parkinson's disease (PD) receiving dopamine agonists.[131] In 26,814 users of anti-parkinsonian drugs, the incidence rate of HF increased with the current use of any dopamine agonist (1.58, 1.26-1.96), particularly with pramipexole (1.86, 21-2.85) and cabergoline (2.07, 1.39-3.07), but not with ropinirole or

pergolide, compared with no use.[132] In another cohort of 25,459 PD patients, among non-ergot dopamine agonists, only pramipexole was associated with an increased risk of HF (1.61, 1.09-2.38), especially in the first three months of therapy and in patients aged 80 years and older.[133] Thus, in 2012 the FDA warned of a possible increased risk of HF with pramipexole use in PD patients. The use of non-ergot dopamine agonists in PD patients was not associated with an increased risk of HF, nor was it shown to increase the overall mortality or the risk of MACE compared to the PD patients on monotherapy with levodopa alone.[134]

Combination of SSRI and Beta-Blockers

Selective Serotonin Reuptake Inhibitors (SSRIs) present a low rate of adverse cardiovascular effects and even in patients with HF, post-MI, or unstable angina, they exert minimal effects on echocardiographic indexes of cardiac function.[135,136] However, FDA does not recommend citalopram in patients with uncompensated HF.

SSRIs can inhibit the activity of several cytochrome P450 enzymes, which increases the exposure of several pharmacological classes, such as antiarrhythmics, beta-blockers, antihistamines, and CCBs.

Coadministration of SSRIs and β-blockers was significantly associated with a higher risk of overall and cardiovascular death compared with coadministration of β-blockers and tricyclic antidepressants.[137] SSRIs inhibit CYP2D6 which mediates metoprolol biotransformation. Fluoxetine, norfluoxetine, and paroxetine are potent inhibitors of the *in vitro* metabolism of metoprolol, suggesting a possible *in vivo* interaction.[138] Fluvoxamine, sertraline, and citalopram are less potent inhibitors.[138] Thus, fluoxetine should not be co-administered with metoprolol in HF.[137]

Lithium

It is the treatment of choice for the long-term control of mania and to prevent relapse in bipolar disorder, but presents a narrow therapeutic index and has been infrequently associated with severe cardiac side effects.[139] In a small study, five patients developed oedema and two of them developed new-onset HF during lithium carbonate use.[140] Lithium is contraindicated in HFrEF patients.

VI) General anaesthetic PIP-HFrEF items

HF patients have a diminished cardiac reserve capacity that may be further compromised by anaesthesia.[141] Elderly patients with HF who undergo major surgical procedures have substantially higher risks of operative mortality and 30-day all-cause readmission among patients with HF compared with patients with CAD and patients with neither HF nor CAD.[142] Most anaesthetics can exert a direct myocardial depression and affect some hemodynamic mechanisms (i.e. heart rate, preload, afterload, and peripheral vascular resistance).

Intravenous Anaesthetics

Etomidate is a short-acting anaesthetic that causes the least cardiovascular depression, being primarily used for anaesthesia induction in cardiac-compromised patients.[141] However, it is not suitable for the maintenance of anaesthesia as its prolonged use suppresses the adrenocortical functions.

Ketamine is a dissociative anaesthetic, with a direct negative inotropic and vasodilator effects that are counteracted by a sympathomimetic action related to both central and peripheral catecholamine reuptake which increases arterial pressure, heart rate, and cardiac output. However, in patients with significant LVSD, the sympathetic stimulation may not be adequate to overcome the negative inotropic effects, resulting in hemodynamic instability.[141] Ketamine

also increases myocardial O_2 consumption. Thus, it is not the appropriate drug in patients with CAD, hypertension, tachycardia, or HF.

Propofol is a short-acting agent widely used for both induction and maintenance of anaesthesia. Propofol produces negative inotropic effects and vasodilatory properties and blunts the baroreceptor reflex reducing sympathetic nerve activity. Propofol reduces systemic vascular resistances, cardiac contractility, and preload.[141] Patients with impaired LV function can poorly tolerate significant reductions in cardiac output because of decreases in ventricular filling pressures and contractility.[143,144]

VII) Glucose-lowering PIP-HFrEF items

Dipeptidyl peptidase-4 inhibitors (DPP-4Is)

The SAVOR-TIMI53 trial randomized patients with type 2 diabetes mellitus (T2DM) at high-risk for cardiovascular events (12.8% with HF) to usual diabetes care plus saxagliptin or placebo. Despite no difference was found in the risk of cardiovascular death, MI or stroke, an unexpectedly higher risk of HF hospitalization was observed in patients treated with saxagliptin *vs*. placebo (HR 1.27, 1.07-1.51).[145] This increase in risk was highest among patients with elevated levels of natriuretic peptides, previous HF, or chronic kidney disease. In 7,620 patients from a national commercially insured U.S. claims database with diabetes and incident HF, sitagliptin was associated with an increased risk of HF hospitalizations (OR 1.84, 1.16 to 2.92), but not with an increased risk of all-cause hospitalizations or death.[146] A meta-analysis of 84 trials suggests that the overall risk of acute HF was higher in patients treated with DPP-4Is as compared with those treated with placebo/active comparators (OR 1.19, 1.03-1.37). When different DPP-4Is were estimated separately, the OR (95%CI) was 0.99 (0.44-2.24), 0.55 (0.20-1.53), 1.22 (1.03-1.45), 1.56 (0.66-3.65) and 1.18 (0.89-1.56), respectively, for sitagliptin,

vildagliptin, saxagliptin, linagliptin and alogliptin, making it difficult to say if this is a class effect or not.[147]

However, in the EXAMINE study, which enrolled 5,380 patients with T2DM and unstable angina, no difference was found in the proportion of patients hospitalized for HF between the alogliptin and placebo groups (HR 1.07; 0.79-1.56).[148] Similarly, in the TECOS trial enrolling 14,671 patients with T2DM and cardiovascular disease, sitagliptin was non-inferior to placebo for the primary composite cardiovascular outcome (0.98; 0-88-1.09) and the rates of hospitalization for HF did not differ between the two groups (1.00, 0.83-1.20).[149] Thus, although it is very unlikely that the observed increase in HF hospitalizations seen with saxagliptin is a class effect of DPP-4Is, close post-marketing vigilance is critically needed to evaluate the cardiovascular safety of this class.[150]

Metformin

Metformin can be prescribed in patients with stable HF if their renal function is normal, but is contraindicated in patients with moderate-severe renal failure (GFR <30 mL/min/1.73 m^2), unstable or decompensated HF or recent MI according to EMA (12/12/2016, EMA/868987/2016).

Use of metformin to treat diabetes now expanded to patients with moderately reduced kidney function. The ESC guidelines on diabetes stated that metformin is safe at all stages of HF with preserved or stable moderately reduced renal function (eGFR >30 mL/min), and results in a lower risk of death and HF hospitalization compared with insulin and sulfonylureas.[151-153]

Unfortunately, prospective data evaluating the safety of metformin in patients with advanced HF, in whom hepatic and renal dysfunction are often encountered, are lacking.

Thiazolidinediones

Rosiglitazone and pioglitazone are peroxisome proliferator-activated receptor gamma agonists, that increase tissue sensitivity to insulin. This class of anti-diabetic medications is not recommended in HFrEF patients.[150,154]

In controlled trials, thiazolidinediones exacerbate existing HF and increase the risk for new-onset HF in patients with T2DM.[155-161,162,72] A meta-analysis of 19 randomised clinical trials including 16,390 patients with T2DM showed a high rate of HF incidence upon long-term therapy with pioglitazone (HR 1.41; 1.14-1.76).[156] In another meta-analysis, among patients with impaired glucose tolerance or T2DM, rosiglitazone use for at least 12 months more-than-doubling of the risk of HF with rosiglitazone (2.09; 1.52-2.88)[157] Similarly, the risk of HF increased in pioglitazone users (HR 1.41; P=0.002).[158] In the PROactive study, pioglitazone was associated with an increased rate of serious HF as compared with placebo (HR 1,41, 1.10-1.80). However, the subsequent event rate of a composite endpoint that included the most serious outcomes associated with HF, i.e., all-cause mortality, MI, and stroke, was proportionately lower in pioglitazone-treated patients with serious HF (0.64, 0.436–0.946).[163]

In the RECORD trial, patients on monotherapy with metformin or sulfonylureas who were randomized to add-on rosiglitazone had twice the risk of HF than those randomized to a combination of metformin with a sulfonylurea.[164] In a pooled analysis of ADOPT, RECORD, and DREAM trials, rosiglitazone was associated with a clear increase in the risk of HF (OR, 2.17; 1.49-3.17).[159] Results showed no heterogeneity of effects across studies *(P for interaction=0.26),* which indicated a class effect for thiazolidinediones. Compared with controls, patients given thiazolidinediones had increased risk for the development of HF across a wide background of cardiac risk (1.47-1.72). Paradoxically, the risk of cardiovascular death was not increased with either of the two thiazolidinediones (0.93, 0.67-1.29).[160,161] The risk of HF was higher with rosiglitazone than with pioglitazone (2.73 [1.46,

5.10] vs 1.51 [1.26, 1.81]).[76] Use of thiazolidinediones was also associated with fluid retention, which may exacerbate or precipitate HF (OR 2.04; 1.85, 2.26).[76] The oedema seems to be refractory to diuretics but promptly respond to withdrawal of therapy. In a systematic review and meta-analysis of published observational studies, the relative risk (RR) of HF in rosiglitazone users versus pioglitazone users was 1.16 (95%CI 1.05-1.28) and the RR for rosiglitazone versus metformin was 1.36 (95%CI 1.17-1.59).[114] Finally, in 227,571 Medicare beneficiaries aged 65 years or older who initiated treatment with rosiglitazone or pioglitazone, the risk of HF was greater with rosiglitazone compared with pioglitazone (HR 1.25; 1.16–1.34).[165] Thus, in the ESC guidelines, rosiglitazone and pioglitazone are contraindicated in patients with HF or history of HF (NYHA stages I to IV).[1,154]

VIII) Miscellaneous PIP-HFrEF items

Anti-hypouricemic agents

Several reports showed the association between the administration of allopurinol or febuxostat and HF development or exacerbation.[166-170] In elderly HF outpatients, febuxostat showed a lower risk of cardiovascular mortality compared to allopurinol in elderly HF outpatients.[171] Thus, the potential risks and benefits when prescribing febuxostat or continuing treatment should be assessed on an individual basis before and after treatment initiation.

Beta$_2$-adrenergic agonists

The prevalence of HF in patients with COPD ranges from 20 to 70%[172] The presence of COPD was associated with increased risk of HF hospitalization (HR 1.56; 95%CI 1.4-2.1) and MACE (1.23; 1.03-1.75) and is often responsible for suboptimal β-blocker use due to fear of inducing bronchospasm.[173] Selective β2-agonists (e.g. formoterol, salbutamol, salmeterol, terbutaline) exert positive cardiac inotropic and chronotropic effects and inhaled β2-agonists are the mainstay in the management of COPD. However, β2-agonist use has been associated with an increased risk of MI, congestive HF, cardiac arrest, and sudden cardiac death.[174-176] The use of

oral β-agonists (OR 3.4, 1.1–11.0) and β-agonist inhalers or nebulization (OR=3.2, 1.4–7.1) increases the risk of idiopathic dilated cardiomyopathy in patients with a history of emphysema or chronic bronchitis.[177] In another study, β2-agonists did not appear to be associated with incident HF but among patients with a history of HF identified a dose-response association between the number of inhaled β-agonists and the risk of hospitalization for chronic HF (≥3 canisters/month: OR 2.1, 1.2-3.8).[174] In the CHARM programme, bronchodilator use was a powerful independent predictor of HF hospitalization (1.49, 1.29-1.72) and MACE (1.32, 1.17-1.76).[178] Data from the ADHERE-EM registry found that acute decompensated HF patients without a history of COPD and bronchodilator use were associated with a greater need for aggressive interventions and monitoring.[179] Furthermore, among 164,494 HF hospitalizations, 53% received acute respiratory therapies during the first 2 hospital days (37% received short-acting inhaled bronchodilators) and this treatment was associated with higher adjusted odds of all adverse outcomes.[180] Moreover, in patients with a hospital discharge diagnosis of HF, the use of any sympathomimetic drug was associated with an increased risk of admission for arrhythmia (4.0; 1.0-15.1), but the risk was higher in patients receiving systemic compared with inhaled formulations.[181]

However, a retrospective analysis of β2-agonist therapy in HF patients showed no relationship with long-term mortality when adjusted for population differences including BNP.[182] Therefore, β_2-agonists must always be used with caution in patients with cardiopathies because these agents may precipitate cardiac diseases. Oral β2-agonists should be avoided in patients with HF, and both the dose and frequency of inhaled therapy should be minimized. Patients with frequent exacerbations or requiring regular inhaled β2-agonists should be switched to an inhaled corticosteroid and/or a long-acting antimuscarinic drug.[183] Also, long-acting β2-agonists increase digoxin-induced cardiac arrhythmias.

Endothelin-1 receptor antagonists and Prostacyclins

They are used in the treatment of pulmonary arterial hypertension. The FIRST trial which recruited HF patients (NYHA III-IV) was terminated early because of a strong trend toward decreased survival in the patients treated with epoprostenol and, therefore, it is contraindicated in patients with HFrEF.[184] In this population, bosentan was associated with no benefit on patient global assessment (the primary endpoint) or mortality, but HF hospitalizations were more common during the first 4-8 weeks of treatment. In a placebo-controlled trial of patients with severe HF, bosentan did not improve the clinical course or natural history of HF as assessed by the risk of death or the combined risk of death or HF hospitalization, but patients on bosentan experienced fluid retention within the first 2-4 weeks and an increased risk of HF hospitalization, despite the intensification of background diuretics.[185]

Fluoroquinolones and Macrolides

The widespread use of macrolides has been accompanied by concerns about their possible deleterious effects on cardiovascular morbidity and mortality.[186-191] In two Danish trials, clarithromycin increased long-term cardiovascular mortality in patients with stable CAD and this increase persisted for three years after discontinuation of the drug.[192,193] The use of clarithromycin in acute exacerbations of COPD or community-acquired pneumonia (CAP) was associated with increased cardiovascular events (HR 1.48, 95%CI 1.13-1.94, and 1.68, 1.18-2.38, respectively).[186] The frequency of congestive HF or LVSD in patients of the COPD cohort was higher in clarithromycin than in non-clarithromycin users (11.4% vs 5.3%). A significant association was found between clarithromycin use and cardiovascular mortality (1.52, 1.02-2.26) but not all-cause mortality (1.16, 0.90-1,51) in acute exacerbations of COPD. However, no association was found between clarithromycin use in CAP and all-cause mortality or cardiovascular mortality. Among patients hospitalized for CAP, erythromycin use was associated with an increased risk of any hospital-acquired cardiac events (1.68, 1.07-2.62), and

HF (2.08, 1.25-3.46).[187] Adjusted HRs for any cardiac event were 0.89 (0.48-1.67) and 1.06 (0.61-1.83) for azithromycin and clarithromycin, respectively.

Levofloxacin and moxifloxacin were associated with a lower risk of HF.[187] HR for erythromycin, compared to beta-lactam monotherapy, on any cardiac event and HF were 1.60 (1.09-2.36) and 1.89 (1.22-2.91), respectively. Intravenous erythromycin use, but not oral azithromycin or clarithromycin use, increases the risk for cardiac events, especially HF, probably because of volume and sodium overload associated with intravenous administration of erythromycin.

Clarithromycin increases digoxin levels and the risk of hospitalization for digoxin toxicity by several mechanisms, including reduction of renal excretion of digoxin, alteration of intestinal flora (*Eggerthella lenta),* and inhibition of cytochrome P-450 in the liver.[194,195] The prescription of clarithromycin at 7, 14, and 30 days prior to the index date was associated with a 4.36- (1.28–14.79), 5.07- (2.36–10.89), and 2.98-fold (1.59–5.63) increase in hospitalization for digoxin intoxication, respectively.[189] Thus, the coadministration of digoxin and clarithromycin should be avoided and that serum digoxin concentrations should be monitored closely when the combination cannot be avoided.

Phosphodiesterase inhibitors (3 and 4)

Concerns have been raised about the safety of phosphodiesterase-3 (PDE-3) and phosphodiesterase-4 (PDE-4) inhibitors in patients with HF.[196-199] Despite its beneficial hemodynamic actions in patients with severe HF (NYHA class III-IV), long-term therapy with oral milrinone increased all-cause (28%; P=0.038) and cardiovascular mortality (34%; P=0.016) and HF hospitalizations.[196] The adverse effect of milrinone was greatest in patients with NYHA class IV (53% increase in mortality; P= 0.006). Patients on milrinone had also

more hospitalizations (44% vs 39%; P=0.041) and serious cardiovascular reactions including hypotension and syncope.[196]

Cilostazol is another PDE-3 inhibitor with antiplatelet, vasodilating, and antiproliferative properties.[200] approved for the treatment of intermittent claudication. In a post-marketing clinical study conducted 1999 through 2003, treatment-related serious adverse events included congestive HF (2%) and tachyarrhythmias.[201] In diabetic patients, a significant association was found between cilostazol and HF hospitalization that persisted after controlling for potential time-varying confounders including drugs potentially associated with HF (OR 1.35, 1.14–1.59).[198] Cilostazol, as other PDE-3 inhibitors, decreases survival in patients with class III-IV HF and is contraindicated in patients with HF of any severity.[199]

Anagrelide is a PDE-4 inhibitor used in the treatment of essential thrombocythemia and for thrombocythemia secondary to myeloproliferative disorders to decrease risk thrombosis and thrombo-haemorrhagic events. Anagrelide has positive inotropic and chronotropic and vasodilatory effects. The development of fluid retention, and less commonly HF with or without the development of cardiomyopathy, has been reported with its use, although controlled data are still very scarce. It may also cause high-output HF reversible upon discontinuation.[202]

In patients with HF, cardiac arrhythmias or electrolytes abnormalities may occur as anagrelide produces hypokalaemia or hypomagnesemia. Therefore, it is important to consider periodic ECG monitoring and electrolyte monitoring. In these patients, a pre-treatment cardiovascular examination, including a baseline ECG and echocardiography is recommended and anagrelide should only be used in patients with known or suspected heart disease when benefits outweigh risks.

IX) Complementary and Alternative Medicines

Alternative medicine is a term that describes medical treatments that are used instead of traditional (mainstream) therapies, whereas the term complementary medicine is used together with conventional medicine. Patients' demand for complementary and alternative medicines (CAM) products is increasing because they perceive these products as natural, relatively low-cost, and probably effective therapies for their diseases.

According to a 2012 national survey, one-third of the US adult population use CAM products, and 42.3% of CAM users did not disclose the use of their most-used CAM modality with their primary care physicians.[203] This nondisclosure was most often due to physicians not asking about CAM products and respondents believing that physicians did not need to know about their CAM use.

A Scientific Statement From the American Heart Association recommended some specific measures concerning these products in patients with HF:[6] i) no nutraceutical or nutritional supplements should be used for the management of HF symptoms or the secondary prevention of cardiovascular events; ii) avoid products with significant interactions with digoxin, vasodilators, β-blockers, antiarrhythmic agents, and anticoagulants, and iii) ephedra-like products (*ma-haung*) should be avoided because of their stimulant effects on blood pressure and heart rate and their increased risk of mortality and morbidity.

X) Over the counter and herbal medicines

More than half of older patients used ≥5 or more prescription medications, as well as OTC medications, herbal medicines and dietary supplements.[20] Several herbal medicines have the potential to interact with HF and/or HF medications, Table 4.

Sympathomimetic decongestants in OTC cold preparations can increase heart rate and blood pressure and increase the risk for cardiac arrhythmias while reducing the efficacy of β-blockers. Also, high doses of OTC NSAIDs may increase the risk of HF worsening and HF hospitalization. Additionally, herb-drug interactions are potentially an important issue for clinicians, particularly in cardiology where the therapeutic window of the prescribed medications is often narrow.[204]

Prevention of PIPHFrEF in practice

The summary of PIPHFrEF items and the recommended strategies for preventing PIP-HFrEF are displayed in Table 5.

Conflict of interest

Authors declare no conflict of interest, except:

Basil S. Lewis, MD, FRCP declared conflicts regarding heart failure as research grants from Novartis, MSD and Bayer Healthcare and personal fees from MSD.

Andrew Coats, MD declares no conflicts related to this work. Outside of this work, in the last 3 years, Professor Coats declares having received honoraria and/or lecture fees from Astra Zeneca, Bayer, Boehringer Ingelheim, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Gore, Impulse Dynamics, Respicardia.

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Table

Potentially Inappropriate Prescriptions in Heart Failure with Reduced Ejection Fraction (PIP-HFrEF)

Position statement on HFrEF specific inappropriate prescribing

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Table 1. Level of Evidence and the magnitude of the medication effect on Heart Failure with reduced ejection fraction.

Level of Evidence
Level of evidence A: Data derived from multiple randomised clinical trials or meta-analyses.
Level of evidence B: Data derived from a single randomised clinical trial or a large non-randomised trial.
Level of evidence C: Data derived from a consensus of experts 'opinions, and/or small studies, or registries.
Medication Effect
Major effect: The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects.
Moderate effect: Effects that can lead to an additional clinic visit, change in NYHA functional class, change in cardiac function, or worsening cardiovascular disease (e.g., hypertension, dyslipidaemia, and metabolic syndrome) or effects that lead to symptoms that warrant a permanent change in the long-term medication regimen.
Minor effect: The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy.

A consensus of the reviewers on the medication effect is based on the effect magnitude, study population sample size, and on the level of evidence that was used in the ESC 2016 guidelines

Table 2. Potentially inappropriate pharmacological agents in Heart Failure.

#	Pharmacological agent	ATC code	$T_{1/2}$ (hour)	Type of interaction	Level of evidence	Effect magnitude	Mortality reports
1	Itraconazole [1-3]	J02AC02	21	Drug-disease interaction: negative inotropic effect of itraconazole. Drug-drug interaction: inhibits the metabolism of Eplerenone, leading to eplerenone toxicity. This combination is contraindicated.	C	Moderate	-
	Amphotericin B [4-7]	J02AA01	24 - 360*	Reversible drug-disease interaction: drug-induced cardiomyopathy and tachycardia exacerbating HF prognosis and may lead to cardiac arrest. Drug-drug interaction: amphotericin B inducing hypokalaemia may cause arrhythmia and potentiate digitalis toxicity.	C	Major	Yes
2	Pregabalin [8-10]	N03AX16	6.3	Drug-disease interaction of calcium channel blockade in all stages of HF NYHA I – IV leading to peripheral oedema.	C	Moderate	-

3	Medicinal formations of High sodium content [11,12]			Evaluation of non-dietary sources need to be considered. Drug-disease interaction in HF and all cardiovascular comorbidities Drug-drug interaction: antagonize the effect of diuretics and natriuretics.	C	Moderate	-
4	Cyclosporine [13,14]	L04A D01	24	Drug-disease interaction by stimulation of the renin-angiotensin system and increase of cardiac afterload.	C	Moderate	-
5	Verapamil (low dose) + Beta-blocker (low dose) combination [15-17]	C08DA01 (verapamil)	2.8–7.4 (verapamil)	Drug-drug interaction: therapeutic duplication of the potent synergistic effect that may provoke a reflex anginal attack, leading to HF exacerbation. Drug-drug interaction: lower achievement of the full benefit of beta-blocker target dose.	B	Moderate	Yes
6	Dronedarone [18,19]	C01BD07	13 – 19	Arrhythmogenic drug-disease interaction causing HF precipitation or exacerbation and symptomatic bradycardia.	A	Major	Yes
7	Febuxostat [20-22]	M04AA03	5 – 8	Drug-disease interaction causing HF precipitation or exacerbation	A	Major	Yes

8	Propranolol [23]	C07AA05	4 – 5	Drug-disease interaction causing HF exacerbation due to the drug negative inotropic and chronotropic effects.	C	Moderate	No
9	Pramipexol [24-27]	N04BC05	8 – 12	Drug-disease interaction causing HF exacerbation			
10	Lithium [28,29]	N05AN01	24 – 36 **	Drug-disease interaction causing HF exacerbation	C	Minor	No

Abbreviations: ATC, WHO Anatomical Therapeutic Chemical Classification System; HF, heart failure; NYHA, New York Heart Association; $T_{1/2}$, elimination half-life.

* Elimination half-life varies according to the formulation of the drug product.

** Longer $t_{1/2}$ in elderly population.

Table 3. Potentially inappropriate pharmacological classes in Heart Failure.

#	Pharmacological class	Type of interaction	Level of evidence	Effect magnitude	Mortality reports
1	Double loop diuretics [30-35]	Drug interaction: unnecessary therapeutic duplication and higher doses of loop diuretics are associated with higher mortality odds.	B	Moderate	Yes
2	ACE-inhibitor + ARB combination (or renin inhibitor) [36-41]	The addition of an ARB (or renin inhibitor) to the combination of an ACEI and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia	B	Moderate	-
3	NDP-CCB in Heart Failure with reduced ejection fraction [17,42,43]	Drug-disease interaction: negative inotropic effect and arterial vasodilation leading to reflex neurohormonal activation and drug-inducing transmembrane potassium movement leading to hyperkalaemia Drug-drug interaction with β-blockers leading to significant negative inotropic effects	A	Moderate	-

4	α1-blockers: doxazosin [44,45]	Drug-disease interaction leading HF precipitation or exacerbation and mortality via possible β1-receptor stimulation with increases in renin and aldosterone secretion.	C	Moderate	Yes
5	Class I antiarrhythmics [46-49] • Disopyramide • Flecainide	Drug-disease interaction: negative inotropic and proarrhythmic effect causing mortality in HF and post-myocardial infarction	A	Major	Yes
6	Class III antiarrhythmic drugs [18,19,50,51] 1) Dronedarone 2) Sotalol				
7	NSAIDs (including COX-2 inhibitors) [40,52-55]	Drug-disease interaction with higher odds of cardiovascular adverse reactions and mortality in presence of ACE-inhibitors with/without loop diuretics.	A	Major	Yes
8	SSRI + Beta-Blocker combination [56]	Uncertain direct drug-drug interaction.	C	Minor	Yes
9	Corticosteroids (glucocorticoids and mineralocorticoids) [5,57-60]	Drug-disease interaction: Immediate increase of sodium and fluid retention and increased risk of hypertension.	B	Moderate	-

		Drug-drug interaction: Adverse drug reactions antagonistic to GDMT effects			
10	Dipeptidyl peptidase-4 inhibitors [61-65] Saxagliptin & Sitagliptin	Uncertain drug-disease interaction leading to HF induction Drug-drug interaction: by increasing the risk of angioedema	B	Major	-
11	Metformin in unstable or end-stage kidney dysfunction [66-68]	Drug disease interaction: metformin causes tissue hypoxia leading to lacto-acidosis which will worsen HF. However, metformin use was not associated with an increased risk for lactic acidosis			
12	Thiazolidinediones (-glitazones) [69-75]	Drug-disease interaction: immediate increase of sodium and fluid retention as well as calcium channel blockade Thiazolidinediones are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization	A	Major	-
13	Macrolides and Fluoroquinolones [76-81]	Drug-disease interaction: both classes precipitate and exacerbate HF Drug-drug interaction: with digoxin leading to digoxin toxicity	B	Major	-

14	Sympathomimetics (e.g., nasal decongestants, appetite suppressants) [82,83]	Drug-disease interaction leading HF precipitation or exacerbation Drug-drug interaction: antagonists to HF GDMT.	A	Major	-
15	Neuroleptics [84-89]	Drug-disease interaction leading HF precipitation or exacerbation, cardiomyopathy, or sudden cardiac death with the highest odds for clozapine.	B	Major	Yes
16	Phosphodiesterase inhibitors (3 and 4) [90-92]	Paradoxical drug-disease interaction due to the ventricular tachyarrhythmia side effect and leading to high rehospitalization and mortality odds on the long-term.	A	Major	Yes
17	Beta-2 agonists [93-95]	Drug-disease interaction: On high doses, beta-2 agonists may lose selectivity and cause beta-1 receptors activation that may lead to HF exacerbation. Drug-drug interaction: the can antagonize the effects beta-blockers in patients with HF	B	Major	-
18	TNF-α inhibitors (TNFi) (Adalimumab, Etanercept, Infliximab) [96, 97, 98]	FDA warns against using TNFi in HF patients based on worsening of congestive HF with TNFi in the Adverse Event Reporting System database	C	Moderate - Low	-

Abbreviations: ACE, angiotensinogen-converting enzyme; ARB, angiotensin-II receptors blocker; GDMT, guideline-directed medical therapy; HF, heart failure; NDP-CCB, non-dihydropyridine calcium channel blocker; NSAIDs, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitor; TNFi, TNF-α inhibitors.

Table 4. List of Potential Interactions of Herbal Products in Heart Failure.

Herbal medicine	Purported use	Possible interaction
Aloe vera (*Alloe barbadensis Miller*)	Wounds and skin disorders (topical), constipation	Causes hypokalemia*
Black cohosh (*Actaea racemosa*, syn. *Cimicifuga racemosa*)	Menopausal disorders, painful menstruation, uterine spasms, vaginitis.	Decrease efficacy of diuretics
Blue cohosh (Caulophyllum thalictroides	Hot flashes and other menopausal symptoms; menstrual cramps and premenstrual syndrome, and to induce labor.	Contains vasoactive glycosides Increases the effects of digoxin May decrease the effects of antihypertensives
Chase tree (*Vitex agnus castus*)	Premenstrual symptoms	Increases effects of β-blockers
Dandelion (*Taraxacum officinale*)	Diuretic, laxative, improve upset stomach	Increase effects of diuretics
Danshen (*Salvia Miltiorrhiza*)	Angina, hyperlipidemia, and acute ischemic stroke	Increases effects of digoxin. Interferes with digoxin assays (falsely high SDC)
Ephedra, Ma huang (*Ephedra sinica*)	Asthma, weight loss	It should be avoided Increases digitalis toxicity Decreases effects of β-blockers
European elder (*Sambucus nigra)*	Flu, colds, constipation	Additive diuretic effect
Fumitory (*Fumaria officinalis*)	Eczema and other eruptions of the skin, cholagogue, mildly diuretic, laxative	Increases effects of β-blockers, CCB and digitalis
Ginseng (*Eleutherococcus senticosus*)	Increase overall body tone, boost the immune system	Interferes with digoxin assay (falsely increased levels)
Gossypol (*Gossypium sp*.)	Male contraceptive	Increases effects of diuretics Hypokalemia*
Grapefruit juice	Weight loss	Increases effects of CCB Modes increase in SDC
Green tea (*Camelia sinensis*)	Improve mental alertness, relieve digestive symptoms and headaches, weight loss	May decrease SDC Reduces exposure to nadolol
Hawthorn (Crataegus oxyacantha *L.)*	Congestive HF, hypertension, angina, atherosclerosis	Increases SDC

		Increases the vasodilator effect of CCB and nitrates
Licorice (*Glycyrrhiza glaba*)	Digestive fumitoryproblems, menopausal symptoms, cough, bacterial and viral infections	Fluid retention, hypokalemia*. Potentiates the effects of spironolactone and digoxin
Lily of the valley (*Convallaria majalis*)	Heart failure	Increases effects of β-blockers and digitalis
Nettle (*Urtica dioica*)	Benign prostatic hyperplasia	Increases effects of diuretics
Night-blooming cereus (*Selenicereus grandiflorus*, Cactus grandiflorus)	Angina), fluid retention associated with heart failure, heart stimulant	Increases effects of ACEI, β-blockers, CCB and cardiac glycosides
Peppermint oil (*Mentha x piperita*	Irritable bowel syndrome, digestive problems, common cold, headaches	Increases digoxin toxicity
Pumpkin seed (*Curcubita pepo*)	Benign prostatic hyperplasia, diuretic	Increase effects of diuretics
Senna (*Cassia senna*)	Chronic constipation	Produces hypokalemia*
St. John's wort (*Hypericum perforatum*)	Mild-moderate depression	Decreases SDC Reduces the effectiveness of CCBs
Yohimbine (*Pausinystalia johimbe*)	Erectile dysfunction	Decreases effectiveness of ACEIs and β-blockers

Plant sources of cardiac glycosides (increase the effects of digoxin)	
Adonis (*Adonis microcarpa, A. vernalis*	Lily of the valley (*Convallaria majalis*)
Balloon cotton (*A. friticosa*)	Oleander (*Nerium oleander*)
Black hellebore (*Helleborus niger*)	Redheaded cotton bush (*Asclepias curassavica*)
Black Indian hemp (*Apocynum cannabinum*)	Rubber wine (*Cryptostegia grandiflora*)
Cactus grandiflorus (*Selenicerus grandiflorus*)	Sea mango (*Cerebra manghas*)
Common oleander (*Nerium oleander*)	Squill (*Urginea maritima, U. Indica*)
Dogbane (*Apocynum cannabinum*)	Strophantus (*Strophanthus hispidus, St. kombe*)
Foxgloves (*D. Purpurea, D. Lanata*)	Yellow oleander (*Thevetia peruviana*)
Frangipani (*Plumeria rubra*)	Wallflower (*Cheiranthus cheiri*)
King's crown (*Calotropis precera*)	Wintersweet (*Carissa spectabilis*)

ACEI, angiotensin-converting enzyme inhibitors; CCB, calcium channel blocker; SDC: serum digoxin concentrations

* Hypokalemia increases the risk of digitalis toxicity.

Table 5. Summary of PIPHFrEF practical considerations and the recommended strategies for PIPHFrEF reduction in HF practice settings

Summary of Practical Considerations	PIP-HFrEF reduction strategies
1. The addition of an ARB (or renin inhibitor) to the combination of an ACE inhibitor and an MRA is not recommended in patients with HF, because of the increased risk of renal dysfunction and hyperkalaemia. The use of ACE inhibitor/ARB combination should be restricted only to symptomatic HFrEF patients receiving a beta-blocker, but who are unable to tolerate an MRA and must be used under strict supervision by the cardiologist. 2. There is a higher safety profile for bisoprolol, metoprolol, and nebivolol in HF patients with COPD than for carvedilol. 3. The co-administration of β-blockers with other antiarrhythmic agents increases the risk of hypotension, bradycardia, and AV block and can precipitate HF. Thus, close monitoring of patient's ECG, heart rate and blood pressure is highly recommended. 4. In patients already taking β-blockers, the necessary addition of dronedarone requires the performance of ECG and dose adjustment of beta-blocker dose upon dronedarone initiation. 5. Dronedarone increases plasma digoxin concentrations and exerts a synergistic effect on heart rate and AV conduction. If digoxin treatment is continued, the dose of digoxin should be halved, and close monitoring of the patient's ECG and digoxin plasma levels are recommended. 6. The coadministration of non-dihydropyridine CCB and dronedarone is contraindicated in HF patients. Both PIP-HFrEF items should not be used in HF either as single or combined.	1. Patients should be informed of the signs and symptoms of congestive HF and advised to consult their healthcare provider if they develop or experience signs or symptoms of HF worsening, such as weight gain, dependent oedema, or increased dyspnoea. 2. To minimize the negative impact comorbidities, appropriate attention and multidisciplinary team integration should be used to identify, prioritize, and manage cardiovascular and non-cardiovascular conditions. 3. The physician should assess the severity and impact of comorbidities and review the medications currently taken regularly, including prescribed, OTC medications, and CAMs. 4. For better delivery of physician's instructions, clinical pharmacists should be empowered in the management of medication therapies particularly, when medications for comorbidities are prescribed and adjusted by different clinicians, many times, with minimal consideration for drug-drug, drug-disease interactions, and target dose achievement. [99-102] In addition to optimization of patient's adherence, Clinical pharmacists can identify inappropriate (including under-prescription and under-dosing), unnecessary, and/or potentially hazardous medications that could exacerbate HF. [12,100,103-118] 5. Community Pharmacists can act as the first checkpoint for PIPHFrEF screening in community-dwelling HF patients. When community pharmacists are involved in the healthcare loop, patients experiencing a nascent episode of worsening HF could well be identified and their physicians alerted before it might otherwise have been detected and while there is an early opportunity to effectively intervene. The community pharmacists are well-positioned to play many essential roles in HF management on the levels of review of medications, polypharmacy appropriateness, medication reconciliation, patient education about the severity of

7. Non-dihydropyridine CCBs (diltiazem or verapamil) should be avoided in patients with HFrEF, as they increase the risk of HF worsening and HF hospitalization.

8. The combination of diuretics acting at a different site to produce a *sequential nephron blockade* allows obtaining an additive diuretic effect in patients with severe HF or refractory oedema. This combination is preferred to higher doses or a combination of two loop diuretics.

9. The antihypertensive drugs doxazosin, minoxidil and moxonidine are contraindicated in HF patients.

10. Regular monitoring of blood pressure, lipids profile, and serum potassium levels are recommended when cyclosporine is coadministered with potassium-sparing drugs (e.g. potassium-sparing diuretics, ACE inhibitors, ARBs) or potassium-containing medicinal products.

11. Concurrent administration of itraconazole with calcium channel blockers (CCBs, dihydropyridines, and verapamil) or statins (atorvastatin, lovastatin, simvastatin) should be carried out under strict caution in HF patients and their dosage should be reduced under close monitoring of the healthcare provider. Also, the combination of itraconazole and eplerenone is contraindicated in HF patients.

12. Glucocorticoid excess increases fluid retention, induces cardiovascular risk factors (obesity, insulin resistance, glucose intolerance, dyslipidaemia, and hypertension), accelerates the progression of atheromatous vascular disease, and increases the incidence of HF.

13. Pramipexole (DA agonist) is not recommended in PD patients having or at risk of HF.

14. Citalopram SSRI is not recommended in HF patients.

the disease itself, and appropriate administration of medications at home, as well as increasing the adherence and compliance levels of the patients. [100,119-122]

6. The potential risks and benefits of each medication should be assessed before the initiation of treatment in order to select safer and more effective alternatives, rationally. The benefit/risk assessment should take into consideration the severity of HF, dosing regimen, and individual risk factors for HF development, precipitation, or exacerbation.

7. Healthcare providers should recognize the basic mechanisms by which medications can exacerbate or cause HF such as sodium retention, negative inotropic effect, and direct cardiotoxicity as well as bad lifestyle behaviours.

8. Healthcare providers should conduct comprehensive medication reconciliation at each clinical visit and with each admission and identify significant drug interactions, among medications used to treat HF and any other comorbidities.

9. It is highly recommended to avoid or discontinue the PIP-HFrEF item as soon as possible. In some instances, this intervention is not possible, therefore particular caution and close monitoring are highly recommended in such types of HF patients. The recovery of myocardium mainly depends on the offending PIP-HFrEF item half-life.

10. Awareness that the pharmacokinetics parameters of PIP-HFrEF items can be significantly changed during acute overload state or old age, which may cause gut oedema, hepatic congestion, and/or renal insufficiency.

11. The prescription of safer pharmacological alternatives is highly recommended for better clinical outcomes. For instance, several agents should be considered as contraindicated in HF patients such as diltiazem, verapamil, disopyramide, flecainide, dronedarone, and propafenone. Compared to non-dihydropyridine CCB, amlodipine and felodipine showed higher safety profile in patients with HFrEF, and they can be used only if there is no other safer alternative for patients with HFrEF. [123,124] Also, HF patients with diabetes should be appropriately treated, similar to diabetic patients without HF. [125] However, some diabetes causing complications may influence the selection of antidiabetic medications, target dose achievement, and therapeutic drug monitoring. Nowadays, SGLT2

15. Fluoxetine should not be co-administered with metoprolol in HF.
16. Rosiglitazone and pioglitazone are contraindicated in patients with HF or history of HF (NYHA stages I to IV).
17. Ketamine is not the appropriate drug in patients with coronary artery disease, hypertension, tachycardia, or HF.
18. Oral β2-agonists should be avoided in patients with HF, and both the dose and frequency of inhaled therapy should be minimized to the lowest therapeutic dose.
19. It is preferred to switch HF patients with frequent respiratory exacerbations or requiring regular inhaled β2-agonists to an inhaled corticosteroid and/or a long-acting antimuscarinic drug.
20. Long-acting β2-agonists increases the digoxin-induced cardiac arrhythmias.
21. Cilostazol, as other PDE-3 inhibitors, decreases survival in patients with class III-IV HF and its use is contraindicated in patients with HF of any severity.
22. The coadministration of digoxin and clarithromycin should be avoided and that serum digoxin concentrations should be monitored closely when the combination cannot be avoided.
23. Cyclosporine increases exposure to digoxin and statins (atorvastatin, pitavastatin, simvastatin).
24. Digoxin plasma levels are increased by amiodarone, dronedarone, flecainide, propafenone, quinidine, and verapamil, and propafenone increases the plasma levels of propranolol and metoprolol.
25. All NSAIDs or COX-2 inhibitors are not recommended in patients with HF, as they increase the risk of HF worsening and HF hospitalization.

inhibitors (e.g. Dapagliflozin) showed a statistically significant reduction in the risk of HF worsening, symptoms burden, and clinical outcomes. [125] On the other side, better utilisation of the NSAIDs alternatives according to the presenting indication is highly recommended for the sake of patients' prognosis. For instance, in osteoarthritis management in the presence of HF, non-pharmacological measures and conventional pharmacological medications would be better options for HF prognosis and clinical outcomes.

12. It is better to avoid the use of OTC medications and CAMs with uncertain efficacy and safety.
13. It is very reasonable to discontinue any medication that does not have a clear indication or has a contraindication with HF GDMT. [38,101,102]
14. Surveillance for medications' effects that are altered by age or HF progression. For example, the volume of distribution tends to decrease for certain HF medications (e.g., digoxin) as HF advances as well as with ageing or renal failure. Lower load and maintenance dosing may be required to avoid an increase in the risk of medication toxicity.
15. Heart failure patients and their caregivers should receive comprehensive education by their physicians and pharmacists about their prescribed medications, over the counter medications, and herbal supplements. They should also receive information about medications list that should be avoided particularly, cold and flu medications, NSAIDs, and antimicrobials that are frequently prescribed by non-cardiologists in primary care settings. Early detection and management of PIP-HFrEF may prevent unnecessary hospitalization or mortality.
16. Risk factors should be comprehensively assessed upon prescribing a PIP-HFrEF item and before drug administration. Meanwhile, significant efforts should be made and social support should be exerted to minimise or eliminate the modifiable risk factors for HF worsening, including smoking, alcohol and illicit drug use, drug-drug interactions, food-drug interactions, medication adherence, and medication errors.

26. Lithium is contraindicated in patients with severe cardiovascular disease.	17. A realistic and clear therapeutic plan should be designed, documented, and engaging patients (and caregivers) as active participants in the care journey, provided with achievable therapeutic goals. [105,126]

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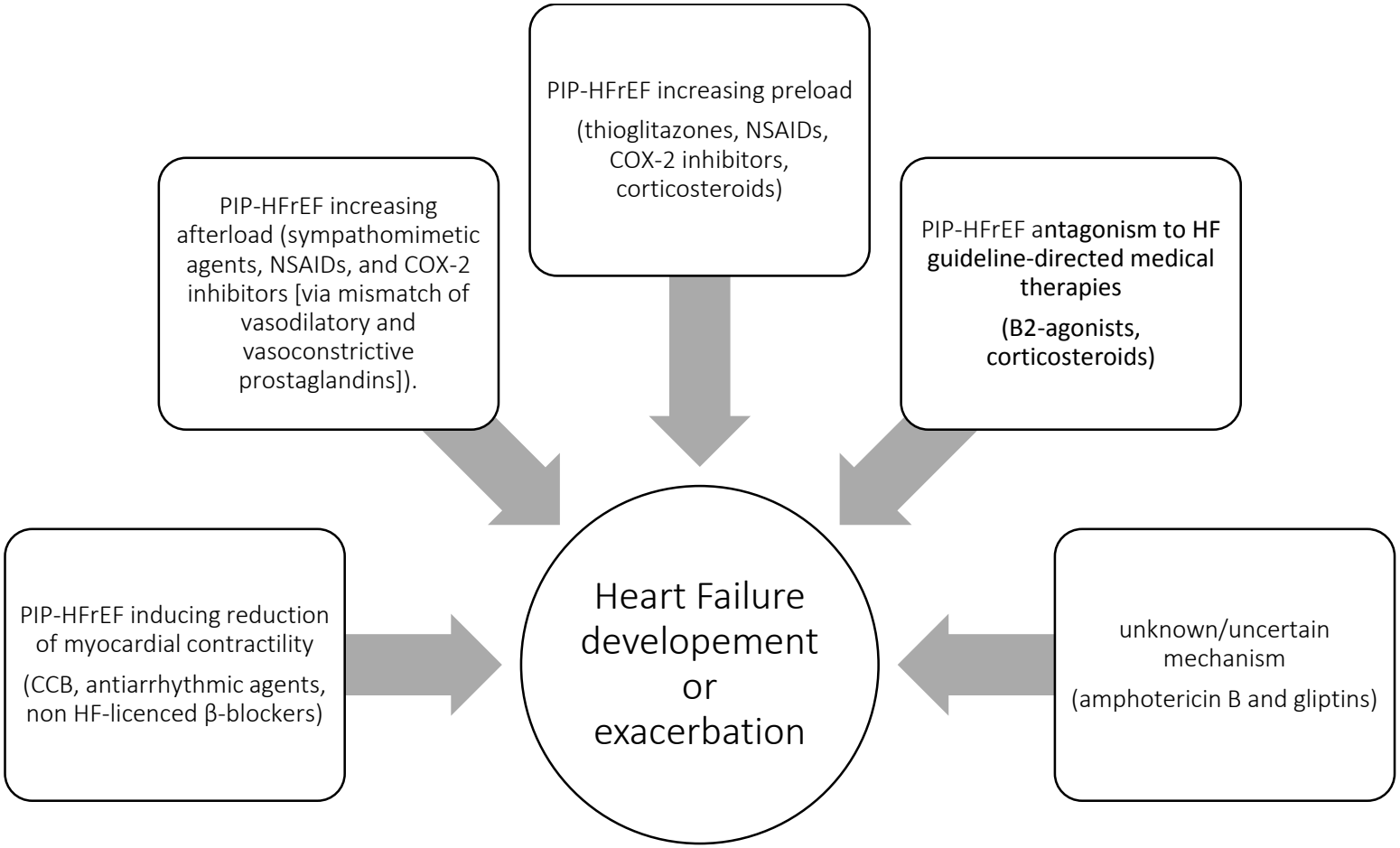
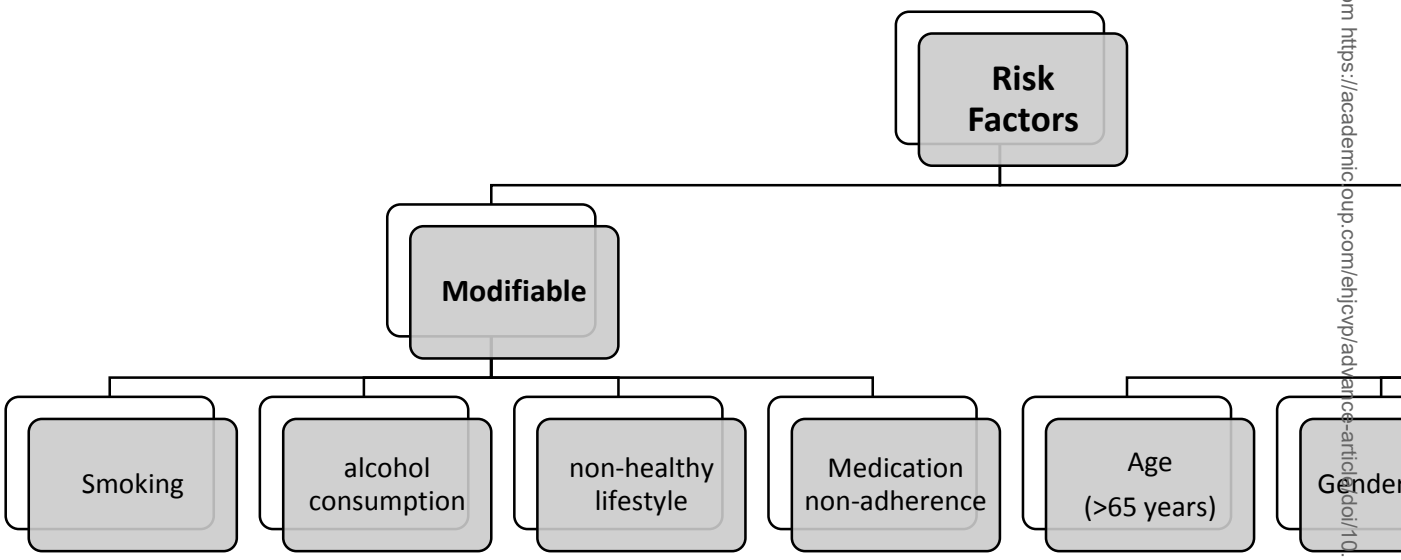
Figure 1. Mechanisms of PIP-HFrEF inducing Heart Failure Precipitation or Exacerbation.



Categories of the pharmacological mechanisms by which many PIP-HFrEF items can induce or exacerbate HF.

Abbreviations: CCB, calcium channel blocker; HF, heart failure; NSAIDs, non-steroidal anti-inflammatory drugs; PIP-HFrEF, potentially inappropriate prescribing in heart failure with reduced ejection fraction.

Figure 2. Risk factors predisposing PIP-HFrEF



The modifiable risk factors represent a major global healthcare challenge and may contribute to the incidence of serious PIP-HFrEF related complications.

Revised version Word count:

The authors did their best to cut down the number of words while keeping the integrity and comprehensiveness of the manuscript content and key messages. The authors removed many parts and converted some texts into tables and figures.

The word count has decreased from **11,649** to **8,486**.

So the authors team would be very grateful if the editorial exceptionally and kindly could accept the current version.