
بسم الله الرحمن الرحيم

Clinical Pharmacy consideration in HF Patients

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REVIEW

Disease management

Potentially inappropriate prescriptions in heart failure with reduced ejection fraction: ESC position statement on heart failure with reduced ejection fraction-specific inappropriate prescribing

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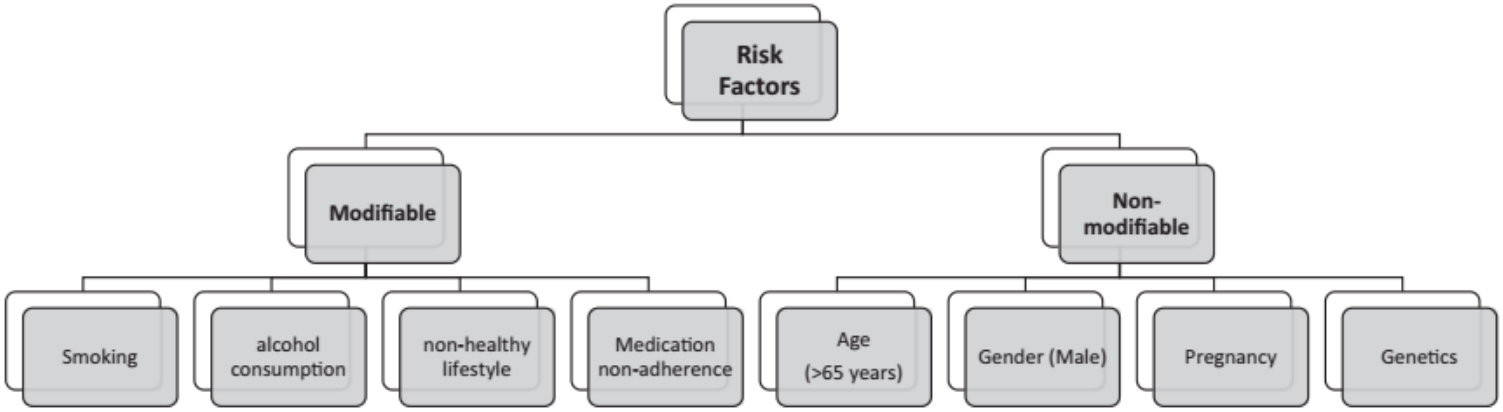

Figure 2 Risk factors predisposing PIP-HFrEF. The modifiable risk factors represent a major global healthcare challenge and may contribute to the incidence of serious PIP-HFrEF related complications.

Antiarrhythmic drugs: Class I

- Most antiarrhythmic drugs (mainly Class I drugs, i.e. sodium ion(Na+) channel blockers, such as disopyramide and flecainide) decrease cardiac contractility and may induce or worsen congestive HF.
- Mechanism: blockade of the L-type calcium ion (Ca2+)

Class II: Beta-Blockers

- 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.

Class II: Beta-Blockers

- Beta-blockers used to treat glaucoma, mainly **timolol**, are generally safe, but can be absorbed systemically to induce bronchospasm, heart block, and decompensate HFrEF. Caution should be taken when ophthalmic b-blockers are administered to elderly patients or patients with contraindications to systemic b-blockers.
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- The co-administration of b-blockers with other antiarrhythmic agents increases the risk of hypotension, bradycardia, and atrioventricular (AV) block and can precipitate HF.
- Its co-administration with digoxin increases the risk of bradycardia and AV block. Thus, close electrocardiogram (ECG) and blood pressure monitoring is highly recommended.
- Intravenous b-blockers should not be given to patients treated with verapamil, whereas verapamil may increase the plasma concentrations of metoprolol and propranolol.

Class III

- Sotalol significantly depress cardiac contractility and exacerbate HF, 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.

- Dronedarone: The ANDROMEDA trial examined the effect of dronedarone on death and hospitalization for HFrEF in patients hospitalized with new or worsening HF.
- Increased early mortality as compared with placebo (8.1% vs. 3.8%; P = 0.03) which was predominantly related to worsening of HFrEF
- Dronedarone: The PALLAS trial studied in permanent atrial fibrillation and additional risk factors : HF, CAD, prior stroke, patients > _75 years with hypertension and diabetes.
- 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

Class IV

- CCBs are generally contraindicated in patients with HFrEF. CCBs inhibit Ca2+ entry through the voltage-gated L-type Ca2
- Diltiazem and verapamil also inhibit CYP3A4 enzymes increasing the plasma concentrations of metoprolol and propranolol which may adversely lead to additive cardiovascular events (e.g. AV block, bradycardia, hypotension, HF)
- The MDPIT trial: Diltiazem in patients with pulmonary congestion increased number of cardiac events (HR 1.41; 1.01–1.96).
- Avoid combination of None DHP CCBs and beta-blocker and antiarrhythmics
- There is only evidence that felodipine and amlodipine can be safely added in patients with HF on standard therapy with uncontrolled hypertension or angina

Amphotericin B

- Infusion-related reactions of Amphotericin-B include chest discomfort, dyspnoea, hypoxia, tachycardia, and hypotension may resolve just upon discontinuation or the end of the infusion,
- 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.
- Cases of new-onset dilated cardiomyopathy with subsequent HF have been reported; symptoms normalized within 6 months of discontinuation.
- Amphotericin B produces hypokalaemia and may potentiate the effects of digoxin

Itraconazole

- Itraconazole is an antifungal agent with negative inotropic effects
- reports of cardiotoxicity, including new-onset and worsening HF, peripheral oedema, and pulmonary oedema
- Daily doses of 400 mg and more
- 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 CCBs (dihydropyridines, diltiazem, and verapamil)
- Also, the combination of itraconazole and eplerenone is contraindicated in HF patients (increase eplerenone concentration)

ACE-inhibitor and ARB combination

- ESC Guidelines dose not recommended ACEI & ARBs combination in HFrEF.
- Increased the risk of hypotension, syncope, decreased renal function (including acute renal failure), and hyperkalaemia. No mortality benefit.

- 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.

High dosing and combination of loop diuretics

- Several studies have addressed the effect of co-administration of two loop diuretic agents in HFrEF.
- 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.

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.
- 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 COPD.

Corticosteroids: doses and incidence of HF

- 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)
- OR 3.69, 3.26–4.18 for high dose (>20 mg prednisolone equivalent daily dose)
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Mineralocorticoids

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

NSAIDs (including COX-2 inhibitors)

- NSAIDs increase renal sodium and water retention, may worsen kidney function, especially in patients with preexisting renal impairment.
- Antagonize the effects of ACE inhibitors/ARBs, diuretics and b-blockers in HF.
- NSAID therapy may double the risk of developing HFrEF
- Patients with renal failure, diabetes, or hypertension might be at a greater risk of developing HF.
- In the Rotterdam study at least one NSAID prescription since diagnosis of HF had a 10-fold increased risk of a relapse [relative risk (RR) 9.9, 1.7–57.0].
- The use of NSAIDs in elderly patients taking diuretics is associated with a two-fold increased risk of hospitalization for HF

NSAIDs vs. COX-2 inhibitors

- In a Danish nationwide population of 36 354 ambulatory HF patients, treatment with NSAIDs, both selective COX-2 inhibitors and non-selective NSAIDs were associated with increased mortality and cardiovascular morbidity (hospitalization because of acute MI and HF), with a dose-dependent response.
- 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.
- 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).
- 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

- 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.

TNF-alpha inhibitors

- In a retrospective cohort study of elderly patients with rheumatic arthritis and prior history of HF, TNF-a 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.
- 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).
- 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).
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TNF-alpha inhibitors

- The 2015 American College of Rheumatology treatment guidelines for rheumatoid arthritis recommended that TNF-a 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 (NYHA III/IV)

Central nervous system PIP-HFrEF items

- Carbamazepine (Na+ channel blocker) & pregabaline (unknown mechanism): Reports of LVSD and HF and edema.
- 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).
- Thus, in 2012 the FDA warned of a possible increased risk of HF with pramipexole use in PD patients.
- FDA does not recommend citalopram in patients with uncompensated HF.
- fluoxetine should not be co-administered with metoprolol in HF
- In a small study, five patients developed oedema and two of them developed new-onset HF during lithium carbonate use.
- Lithium is contraindicated in HFrEF patients

Intravenous anaesthetics

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

Dipeptidyl peptidase-4 inhibitors

- HF hospitalization was observed in patients treated with saxagliptin vs. placebo (HR 1.27, 1.07–1.51)
- sitagliptin was associated with an increased risk of HF hospitalizations (OR 1.84, 1.16–2.92).
- A meta-analysis of 84 trials suggests that the overall risk of acute HF was higher in patients treated with dipeptidyl peptidase-4 inhibitors (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.
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Metformin

- Metformin can be prescribed in patients with stable HF if their renal function is normal, but is contraindicated in patients with moderatesevere renal failure (GFR< 30 mL/min/1.73 m2), unstable or decompensated HF or recent MI according to EMA.
- The ESC guidelines on diabetes stated that metformin is safe at all stages of HF with preserved or stable moderately reduced renal function (GFR> 30 mL/min), and results in a lower risk of death and HF hospitalization compared with insulin and sulfonylureas

Thiazolidinediones

- In the ESC guidelines, rosiglitazone and pioglitazone are contraindicated in patients with HF or history of HF (NYHA stages I–IV).
- increase the risk of HF worsening and HF hospitalization

Beta2-Agonists

- Oral b2-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.
- It is preferred to switch HF patients with frequent respiratory exacerbations or requiring regular inhaled b2-agonists to an inhaled cortico-steroid and/or a long-acting antimuscarinic drug.
- Long-acting b2-agonists increases the digoxin-induced cardiac arrhythmias.

PDE-3 inhibitors

- 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.
- long-term therapy with oral milrinone (PDE-3 inhibitor) increased all-cause (28%; P = 0.038) and cardiovascular mortality (34%; P = 0.016) and HF hospitalizations.
- Anagrelide is a PDE-4 inhibitor used in the treatment of essential thrombocythemia and for thrombocythemia secondary to myeloproliferative disorders
- In patients with HF, cardiac arrhythmias or electrolytes abnormalities may occur as anagrelide produces hypokalemia or hypomagnesemia. ECG and electrolyte monitoring

HF drugs and GFR

- Eplerenone contraindicated in GFR<50 ml/min in hypertensive patients and GFR< 30 in HF patients.
- Spironolactone: Not recommended in GFR< 30 in HF patients (Dialysis: 12.5-25mg/day)
- Captopril: 10-50: 75%dose every 12-18hrs
- GFR<10: 50% dose every 24 hours
- Enalapril: in HF GFR< 30mg: initial 2.5 mg/day to increase 2.5 BD as needed (>4 days intervals to max=40mg/day.)
- Lisinopril: in HF GFR< 30mg: Start 2.5 mg/day increase gradually max to 40mg/day

Main HF drugs and GFR

- HCTZ: diminished diuretic effect in GFR<30: GFR<10 Not recommended
- Metolazone no need dose adjustment.
- Indapamide: GFR 10-50 and under 10: 1.25-2.5 mg/day
- Lasix: in GFR< 30: IV doses >160-200 are not additional effect

Thanks for attention