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Review article

The use of β-blockers in patients with heart failure and comorbidities: Doubts, certainties and unsolved issues

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ABSTRACT

β-blockers represent a mainstay in the pharmacological approach to patients affected by heart failure with reduced ejection fraction (HFrEF). However, underuse of this class of drugs is still reported, especially in the presence of cardiovascular and non-cardiovascular comorbidities, even if they are not contraindications for prescription of a β-blocker. The prognostic benefit of β-blockers is relevant in the presence of comorbidities, and achievement of the maximum tolerated dose is an important goal to increase their favorable prognostic role. The aim of the present review is to analyze the available evidence on the use of β-blockers in HFrEF patients with the most common comorbidities. In particular, we will discuss the role and most appropriate beta-blocker in patients with pulmonary disease (bisoprolol, metoprolol, nebivolol), diabetes (carvedilol and nebivolol), atrial fibrillation (all indicated for rate control, with metoprolol as the first choice followed by bisoprolol, nebivolol, and carvedilol), erectile dysfunction (bisoprolol and nebivolol), peripheral arterial disease (nebivolol), and other conditions, in order to clarify the correct use of this class of drugs in the clinical practice.

1. Introduction

The use of β-blockers is a mainstay in the pharmacological treatment of patients affected by chronic heart failure (HF) with reduced ejection fraction (HFrEF) [1]. Four β-blockers are indicated in this setting, carvedilol, bisoprolol, metoprolol, and nebivolol, which differ in their peripheral vascular effects and selectivity for adrenergic receptors, with being carvedilol a non-selective drug and the remaining three β1-selective agents [1] (Table 1). Randomized clinical trials [2-7] have reported a favorable prognostic impact of treatment with β-blockers in HFrEF, in terms of overall mortality, cardiovascular (CV) mortality, and HF hospitalization (HHF), and the most recent European guidelines [1] recommend their use as first-line therapy in patients with reduced systolic function. Similarly, real-world data have confirmed the positive prognostic impact that β-blockers have on treatment of HFrEF, with no prognostic differences according to selectivity, but with a relevant prognostic role of achieving the maximum tolerated dose [8]. Some concerns still exist on the use of β-blockers in HF patients who also present with relevant comorbidities, due to a potential negative effect of these drugs on symptoms, quality of life, and progression of the comorbid condition. CV and non-CV comorbidities are highly prevalent in HF patients and significantly impact disease progression and long-term prognosis. A recent prospective cohort study [9] reported that in HFrEF patients with multiple comorbidities higher doses of β-adrenoceptor antagonist were associated with lower rates of all-cause mortality, progressive HF, and sudden death (Fig. 1). Thus, optimized pharmacological HF treatment is of crucial importance in these patients.

The aim of this review is to summarize the current evidence on the use of β-blockers in HFrEF patients with specific CV and non-CV comorbidities in order to clarify the currently suggested use of this class of drugs in the clinical practice and, when possible, the choice of a specific β-blocker according to clinical criteria.

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Table 1
β-blockers and doses recommended for treatment of HFrEF.

	AR activity	Initial dose (mg/day)	Target dose (mg/day)
Bisoprolol	β1-selective	1.25 mg	10 mg
Carvedilol	β1-β2-α	6.25 mg	50–100 mg
Metoprolol	β1-selective	12.5–25 mg	200 mg
Nebivolol	β1-selective	1.25 mg	10 mg

AR, adrenergic receptor.

1.1. The use of β-blockers in CV and non-CV comorbidities: a practical approach

In the following section we provide a practical approach to β-blockers use and single agents' choice in specific HF-associated conditions (Table 3). From a general point of view, independently from the comorbid pattern of the patient, β-blockers maintain their prognostic role in HFrEF and their prescription should be always considered, carefully assessing the presence of contraindications and cautions (Table 2), without, however, being unduly concerned by their use. Moreover, as already discussed, β-blockers need to be titrated to the maximum tolerated dose to achieve their full prognostic benefits. Thus, from a practical point of view, treatment with β-blockers can be initiated at the recommended starting doses (Table 1), proceeding than with dose titration every two weeks, with particular attention to the occurrence of bradycardia (<60 bpm) or symptomatic hypotension (systolic blood pressure <90 mmHg) that may limit further dose increase.

Table 2
Contraindications and cautions for the use of β-blockers. Modified from [1].

Contraindications
- (True severe) Asthma (COPD is not a contraindication – non-severe asthma is a relative contraindication and, in this case, bisoprolol, metoprolol or nebivolol need to be preferred)
- II-degree or III-degree AV block (in the absence of a permanent pacemaker)

Cautions
- Severe/advanced HF
- Current or recent (<4 weeks) worsening HF, heart block, or heart rate <60 bpm
- Persisting signs of congestion, hypotension (systolic <90 mmHg), raised jugular venous pressure, ascites, peripheral edema (try to relieve congestion and achieve 'euvolemia' before starting β-blocker)

COPD, chronic obstructive pulmonary disease; AV, atrio-ventricular; HF, heart failure.

Table 3
Type of β-blocker recommended for patients with HF and comorbid conditions.

Comorbid condition	β-blocker
COPD	bisoprolol, metoprolol, nebivolol
Diabetes	carvedilol, nebivolol
Atrial fibrillation	metoprolol, bisoprolol, nebivolol, carvedilol (in order of preference)
Erectile dysfunction	bisoprolol, nebivolol
Peripheral arterial disease	nebivolol

For β-blocker dose please refer to Table 1.
COPD: chronic obstructive pulmonary disease.

1.2. β-blockers and respiratory comorbidity

Patients affected by HF can present a real respiratory comorbidity independent from the baseline CV condition, such as asthma or chronic obstructive pulmonary disease (COPD), or can manifest impairment of pulmonary function consequent to myocardial enlargement, dysfunction, and congestive status. As subsequently described, the presence of these conditions should not limit the use of β-blockers, except in specific cases, although they can influence the choice a specific agent.

With regards to respiratory comorbidities, COPD is not a contraindication to the use of β-blockers; the only contraindication is severe asthma [1] (Table 2). COPD is highly prevalent in HFrEF patients, being reported in about 30% of cases and, similarly, the prevalence of HF in COPD patients is about 30% [10]. In this setting, however, an epidemiological aspect needs to be considered, since diagnosis of COPD is not always supported by pulmonary function tests, which are available in only about 30% of HF patients [11] and diagnosis is frequently patient-reported, physician-reported, or based on anamnestic or therapeutic data. The presence of COPD negatively influences the prognosis of HFrEF patients, mainly in terms of recurrent hospitalizations, due to both rapid impairment of the hemodynamic balance, as a consequence of COPD exacerbations, and to undertreatment of HF patients and comorbid COPD, primarily in terms of use and titration of β-blockers leading to poor disease control [12-14]. The prognostic relevance of the administration of β-blockers is independent of the presence of COPD at baseline, and achievement of the maximum tolerated dose has a significant prognostic importance even in this setting [15]. Moreover, β1-selective agents (bisoprolol, metoprolol, and nebivolol) should be preferred in COPD patients, since these agents are not responsible for FEV_1 worsening compared to placebo nor for exacerbation of respiratory symptoms, and have no impact on the clinical effects of β-agonists [16, 17]. Considering the single agents, COPD patients treated with bisoprolol exhibit higher FEV_1 values compared to carvedilol and metoprolol (carvedilol 1.85 [95% CI 1.67 to 2.03] l/s; metoprolol 1.94 [95% CI 1.73 to 2.14] l/s; bisoprolol 2.0 [95% CI 1.79 to 2.22] l/s; p <0.001) and the switch from carvedilol to a β1-selective agent leads to significant improvement of FEV_1 [16] (Fig. 2). Moreover, the prescription of a

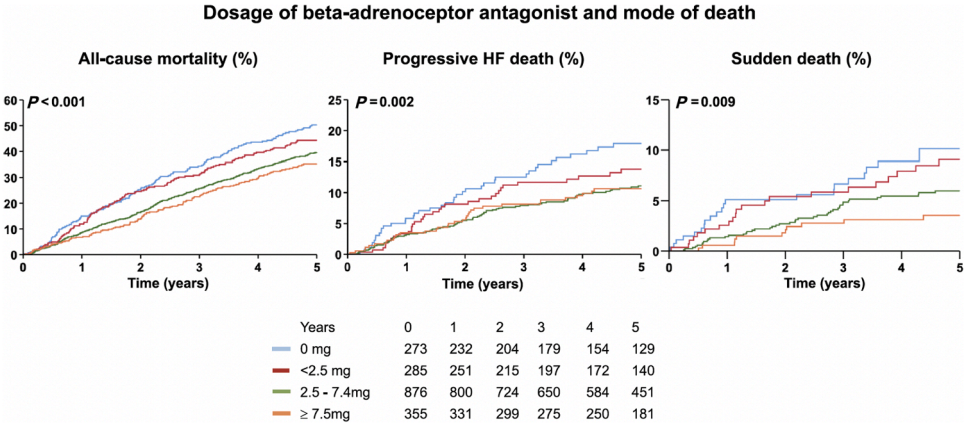

Fig. 1. Kaplan–Meier plots of all-cause mortality, death due to progressive heart failure, and sudden death stratified by bisoprolol equivalent dose of β-blockers. Escalating doses of beta-adrenoceptor antagonists are protective against all three outcomes. Reproduced with permission from [9].

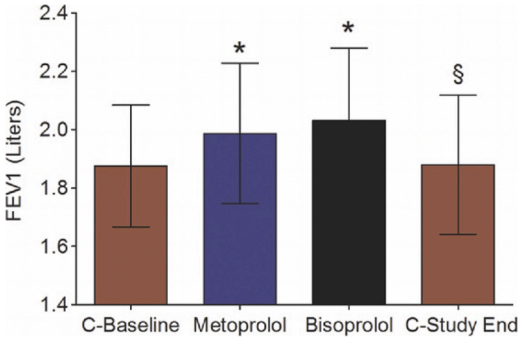

Fig. 2. Switching between the non-selective beta-blocker carvedilol and β1-selective blockers results in clear changes in airway function. Forced expiratory volume in 1 second (FEV_1) in the subgroup of subjects who started the study on carvedilol (C) and relative differences after the switch to metoprolol and bisoprolol. The last bar on the right shows FEV_1 returning to baseline levels on resumption of carvedilol. *$p = 0.02$ compared with baseline; §p=ns compared with carvedilol at baseline and $p = 0.02$ compared with bisoprolol. Reproduced with permission from [16].

non-selective agent, such as carvedilol, has been associated with higher rates of HHF over time compared to selective agents, which is related to both exacerbation of COPD symptoms and to lower treatment persistence and compliance vs. selective drugs [18]. A still unsolved issue is how to manage the use of β-blockers in case of COPD exacerbation; at least half of HHF are related to non-CV reasons, and respiratory diseases contribute to around one-third of them [19]. Only limited data are available on the optimal use of β-blockers during an acute COPD exacerbation; a large retrospective study of 35,082 patients with HF, ischemic heart disease, or hypertension, hospitalized for an acute COPD exacerbation, showed no correlation between treatment with a β-blocker and in-hospital mortality (OR 0.88, 95% CI 0.71–1.09), 30-day readmission (OR 0.96, 95% CI 0.89–1.03), or need for late mechanical ventilation (OR 0.98, 95% CI 0.77–1.24) [20]. However, treatment with non-selective β-blockers, compared to selective agents, was associated with an increased risk of 30-day readmission (OR 1.25, 95% CI 1.08–1.44). COPD exacerbations should not regularly cause discontinuation of β-blockers [20].

Thus, use of a β-blocker is of prognostic relevance in HF patients with comorbid COPD and should be administered, preferring selective agents, such as bisoprolol, metoprolol, and nebivolol, starting with low doses, respectively 1.25 mg od, 12.5–25 mg od, and 1.25 mg od (Table 1), and aiming to achieve the highest possible dose with close monitoring for clinical signs of airway obstruction, and, if needed, instrumental monitoring, especially in complex and elderly patients.

Possible impairment of pulmonary function related to the baseline CV condition should also be considered in HF patients: as left ventricular filling pressure increases, pulmonary congestion and interstitial edema develop, with a consequent reduction of lung volumes and the occurrence of a spirometry restrictive pattern, together with an impairment of lung diffusing capacity [21]. In decompensated HF, an obstructive-like pattern may develop due to bronchial wall edema [21]. Approximately 90% of pulmonary β-receptors are located in the alveoli and are predominantly of the β_2 type (70%). Their stimulation seems to facilitate the removal of alveolar fluid by increasing intracellular sodium transport. Thus, blockage of these receptors by non-selective β-blockers might limit the mechanisms of alveolar fluid clearance and impair lung diffusing capacity. Paolillo et al. [22] demonstrated, in 22 healthy males randomized to treatment with carvedilol or bisoprolol and exposed to rapid saline infusion to over-hydrate the lung and determine interstitial edema, that carvedilol, but not bisoprolol, decreased alveolar-capillary membrane diffusion capacity (−13±7%, $p = 0.001$) and increased capillary volume (+20±22%, $p = 0.016$). In HF patients, the same authors reported, in a β-blocker cross-over analysis, that there is greater impairment in lung diffusion capacity with carvedilol compared to bisoprolol and nebivolol [23]. These observations are likely related to the alveolar β_2-blockade, which is able to downregulate the active pumps located on the alveolar surface that are required to pump fluid out of the alveolar district, thus supporting the hypothesis that β_2-alveolar receptors contribute to alveolar fluid control in humans.

Accordingly, these data support the concept that selective β_1-blockers, in particular bisoprolol as first choice, followed by nebivolol (no current data is available in this setting for metoprolol), should be preferred in HFrEF patients with impaired lung diffusion capacity at baseline, in HFrEF patients prone to congestion, or with frequent exposure to hypoxia (high altitude, airplanes), and in the presence of clinical and/or radiological signs of lung fluid accumulation [24].

1.3. β-blockers and diabetes mellitus

Diabetes mellitus (DM) is a frequent comorbidity in HFrEF with a prevalence ranging from 10 to 30% in chronic patients and up to 40% in hospitalized subjects [25]. A strict bidirectional interaction exists between the two conditions. Patients with DM may develop asymptomatic myocardial dysfunction or overt HF status more frequently than in the general population that is not necessarily related to coronary atherosclerosis, and HF complicates the management and progression of DM over time. In particular, glycemic control over time seems to be the main predictor of prognosis in these patients [26, 27]. In the last years, some concerns have been raised regarding the use of β-blockers in patients with DM due to a possible role of these drugs in masking hypoglycemic signs, such as tachycardia, and to a possible direct hypoglycemic effect of β-blockers. Moreover, a recent observational study [28], together with a post-hoc analysis of the ACCORD study [29], questioned the long-term prognostic benefit of β-blockers in DM, suggesting increased rates of all-cause death in patients on treatment. These data need further confirmation, even if the prognostic benefit of β-blockers in the context of HFrEF is not challenged since β-blockers are as effective in HF-DM patients as in the general HF population [30, 31]. Moreover, as reported in the last guidelines of the European Society of Cardiology (ESC), the treatment benefits strongly support the use of β-blockers in patients with HFrEF and DM [1]. The most recent joint guidelines of the ESC/European Association for the Study of Diabetes (ESC/EASD) [32] propose that the recommendations for pharmacological treatment of HF in the general population can be applied to those with HF and comorbid DM. Thus, β-blockers are recommended (class of Recommendation IA) as first-line therapy for HFrEF to reduce the risk of HHF and death; similarly, β-blockers are recommended in patients with DM after acute myocardial infarction and ejection fraction <40% to prevent sudden cardiac death (class of Recommendation IA) [32]. However, in pre-DM a β-blocker/diuretic combination might favor the development of DM through an effect on insulin sensitivity, and should be avoided for control of hypertension unless required for other reasons [32]. Thus, DM is not a contraindication to β-blockers (Table 2) and β-blockers do not need to be discontinued in patients with DM. In case of uncontrolled glycemia, greater attention needs to be given to DM patients being treated with β-blockers, favoring antihyperglycemic agents with a low risk of hypoglycemia. In this context, the recent recommendations on the use of “new” antidiabetics in DM patients at risk for HF or with an overt HF diagnosis are of utmost importance since these drugs, such as SGLT2 inhibitors, have a very low risk of hypoglycemia and will allow an implementation of use of β-blockers in complex HF-DM patients.

Thus, use of a β-blocker is of prognostic relevance in HF patients with comorbid diabetes and should be administered, preferring agents such as carvedilol and nebivolol because of their ability to improve insulin sensitivity, with no negative effects on glycemic control. No specific dose recommendations for starting β-blockers exist in the context of DM, and the currently suggested dose schema for each agent adopted in the general HF population can also be applied to HF patients with DM, as reported by European HF guidelines (1) (Table 1).

1.4. β-blockers and atrial fibrillation

Atrial fibrillation (AF) is common in patients affected by HFrEF; data from the EuroHeart Failure Survey reported that about 20% of patients with HF exhibit AF and that its prevalence reaches 40% in patients with advanced disease [33, 34]. A bidirectional and complex interaction exits between these two conditions since HF predisposes to AF, and the presence of AF in HF patients significantly worsens symptoms and complicates therapeutic management. AF is also related to prognosis of HFrEF; however, it should be considered as a marker of disease severity rather than an independent prognostic indicator [35]. In the last years, some authors have questioned the use of β-blockers in patients affected by HFrEF. In 2014, Kotecha et al. performed an individual-patient meta-analysis of 18,254 patients, of whom 13,946 (76%) were in sinus rhythm and 3,066 (17%) had AF at baseline [36]. The authors reported that therapy with a β-blocker was associated with significant reduction in all-cause mortality in patients in sinus rhythm (HR 0.73, 95% CI 0.67–0.80; $p<0.001$), but not in patients with AF (HR 0.97, 95% CI 0.83–1.14; $p = 0.73$), with a significant p value for interaction according to baseline rhythm ($p = 0.002$). Similar results were obtained for CV death and hospitalizations, and were confirmed in all subgroups of AF, considering age, sex, ejection fraction, NYHA class, heart rate, and baseline medical therapy [36]. These observations are likely related to the fact that slower heart rates are not associated with improved survival in AF [37], even if prospective studies are still not available, and the most recent ESC guidelines for the management of AF refer that the optimal resting ventricular rate in patients with AF and HF is uncertain, but a rate of <100–110 bpm is usually recommended [38]. In contrast to the above-mentioned meta-analysis, recent sub-studies of randomized trials and real-world data reported that β-blockers have a significant prognostic benefit in patients with AF and HF. In particular, a sub-study of the AF-CHF trial [39], including 1,376 HF patients, performed a propensity-matched analysis considering treatment or not with β-blockers and reported that during a median follow-up of 37 months there was an association between treatment with β-blockers and lower rates of all-cause mortality (HR 0.72, 95% CI 0.54–0.94; $p = 0.018$), but not hospitalizations (HR 0.88; 95% CI 0.71–1.10; $p = 0.223$), irrespective of the pattern or burden of AF. More recently, a sub-analysis of the MECKI score registry [40] on 958 HFrEF patients with AF described that, at 10-year follow-up, patients treated with β-blockers had better outcomes with no differences between β1-selective drugs (53%) and β1-β2-blockers (47%), and that survival improved in parallel with β-blocker dose increase.

Thus, the question is still open and all patients with HFrEF and AF should receive guideline-adherent HF therapy. However, prospective trials are still needed to define the efficacy and prognostic role of long-term therapy with β-blockers in HF-AF patients and to determine the optimal resting ventricular rate in this setting.

The use of a β-blocker still maintains its importance in HF patients with comorbid AF, and β-blockers represent first-choice drugs to control heart rate in AF patients with EF <40%. In this context, metoprolol succinate is the first choice (oral maintenance dose 50–400 mg od), followed by bisoprolol (oral maintenance dose 1.25–20 mg od), nebivolol (oral maintenance dose 2.5–10 mg od), and carvedilol (oral maintenance dose 3.125–50 mg bid) [38]. Higher maximum doses of β-blockers are recommended by AF guidelines for rate control [38] compared to the maximum doses used in the treatment of HFrEF [1] (Table 1). However, it should be always kept in mind that in HF-AF patients a resting ventricular rate of up to 100-110 bpm might still be acceptable [38], and thus such high doses are rarely needed.

1.5. β-blockers and erectile dysfunction

HF shares several risk factors with erectile dysfunction (ED) and the two conditions frequently coexist, with a prevalence of ED in HFrEF of 60–90% [41]. The pathophysiological link between HF and ED is multifactorial, and includes atherosclerosis, traumatic injury, hormonal deficits, medication side effects, and psychogenic influences [41]. Several pharmacological agents used in HFrEF therapy have been related to the presence and worsening of ED and, among these, β-blockers have been historically linked to ED. The reasons for this relationship lie in decreased perfusion pressure, especially on effort, due to the inotropic and chronotropic negative effects of β-blockers, and in a possible direct effect on smooth muscle, even if new agents with a vasodilating action action action might potentially have a favorable effect on ED. Moreover, recent studies have underlined that ED is mostly related to the baseline pathological CV condition rather than to pharmacological treatment, which is mostly negligible.

However, only contrasting data from small studies are available on ED in HFrEF patients. The effect of β-blockers on ED seems to be dose-dependent and more pronounced with non-selective agents. An analysis of 1007 hypertensive patients on β-blockers [42] showed that ED patients received more active medications and were more frequently treated with carvedilol and less frequently with nebivolol. The evaluation of the prevalence and severity of ED considering the individual β-blocker demonstrated that almost 50% of ED patients treated with atenolol, bisoprolol, or nebivolol had mild ED, whereas those treated with carvedilol or metoprolol showed the highest rates of moderate or severe ED [42].

However, in this setting, patients' knowledge and prejudice about the side effects of β-blockers should not be underestimated. A study conducted on 96 patients with newly-diagnosed CV disease, not suffering from ED, reported that ED was present in only 1 patient (3.1%) in the group without knowledge of ongoing treatment, in 5 patients (15.6%) among those who knew that they were receiving a β-blocker, and in 10 patients (31.2%) in the group that was informed about the side effects of the drug ($p<0.01$); sildenafil and placebo were equally effective in reversing ED [43]. Thus, ED has a substantial psychological component and providing correct information to the patient before prescription and during follow-up is needed to avoid detrimental conditioning about the side effects of β-blockers.

The use of a β-blocker maintains its prognostic relevance in HF patients with comorbid ED and should be administered, preferring agents as bisoprolol and nebivolol and starting at the lowest dose, i.e. 1.25 mg for both agents (Table 1). In symptomatic ED patients, even in presence of mild ED symptoms, sildenafil can be prescribed, considering a starting dose of 50 mg to be taken approximately 1 hour before sexual activity; starting from effectiveness and toleration, the dose may be increased, with caution, to the maximum recommended dose of 100 mg. Consider a starting dose of 25 mg in patients >65 years, in patients with severe renal impairment (creatinine clearance <30 mL/minute), and in patients with hepatic impairment (e.g., cirrhosis), because administration of sildenafil in these patients results in higher plasma drug levels.

1.6. β-blockers and peripheral arterial disease

The use of β-blockers in peripheral arterial disease (PAD) is controversial due to their impact on vasomotor tone, potentially leading to worsening symptoms of intermittent claudication. In 2013, a Cochrane intervention review [44] tried to quantify the harmful effects of β-blockers in PAD patients in terms of walking and claudication distance; however, the selected trials included only 119 patients and pooling of trials results was inappropriate since no trials showed a statistically significant worsening effect of β-blockers on the considered outcomes. More recent data from the COPART Registry [45] found that patients hospitalized for severe PAD and treated with β-blockers at hospital discharge did not worsen their outcome (overall mortality, CV mortality or amputation rates) at 1 year compared to patients who were not treated with β-blockers. In HFrEF, the prognostic benefit of β-blockers is undisputed and these drugs, as recommended by European guidelines for PAD [46], are not contraindicated in this setting since they do not alter walking capacity in patients with mild to moderate

PAD. In patients with severe PAD, especially in those with severe limb ischemia, due to the lack of trials, β-blockers should be used with caution with a strict control of worsening of symptoms. With regards to which β-blocker prefer in PAD patients, the vasodilating, endothelium-dependent, NO-releasing properties of nebivolol might be beneficial in this context. The Nebivolol or Metoprolol in Arterial Occlusive Disease Trial [47] found that both nebivolol and metoprolol in patients with intermittent claudication and arterial hypertension were well tolerated and similar in terms of improvement in maximal walking distance during a treatment period of ≈1 year. However, nebivolol showed an advantage vs. metoprolol with a significant improvement in pain-free walking distance [+34% (p <0.003) vs. +17% for metoprolol (p <0.12)].

Thus, use of a β-blocker maintains its prognostic relevance in HF patients with comorbid PAD and should be administered, preferring nebivolol and starting at the lowest dose (1.25 mg), to be up-titrated as in the general HF population, with focused attention on intermittent claudication, especially in patients with advanced disease.

1.7. Other conditions

Age. The only β-blocker specifically tested in patients aged more than 75 years is nebivolol [7], and thus this drug might represent a good choice in older HF patients with normal pulmonary function and lung diffusing capacity [24], and in the absence of other comorbid conditions that could direct the choice on a different β-blocker type.

Hyperthyroidism. Non-selective beta blockers, in particular propranolol, should be prescribed for symptom control in patients with hyperthyroidism because they have a more direct effect on hypermetabolism. However, propranolol is not recommended for the treatment of HFrEF and no current specific recommendation exists on the use of one of the four β-blockers approved for HFrEF in the setting of hyperthyroidism.

Hepatic cirrhosis. Non-selective beta-blockers are the mainstay of treatment for portal hypertension in the setting of liver cirrhosis. In particular, propranolol has been historically used in this setting. However, propranolol is not recommended for the treatment of HFrEF and in patients with both HF and hepatic cirrhosis carvedilol is increasingly used; it seems to exhibit a greater portal pressure reducing effect than propranolol and its use is safe in patients with compensated or decompensated cirrhosis [48].

2. Conclusions

β-blockers are disease-modifying drugs that have a significant impact on the long-term prognosis of patients affected by HFrEF. Accordingly, they are recommended as first-line therapy in the presence of left ventricular dysfunction and need to be titrated to the maximum tolerated dose to achieve their full prognostic benefits . β-blockers are still underused in HFrEF patients affected by complex comorbidities, which, however, do not represent real contraindications to their prescription. Indeed, the presence of comorbidities should not limit the use of β-blockers, and correct knowledge of drug-disease interactions is needed to guide prescription and titration of β-blockers, and in some cases to direct the choice of a specific agent in the individual patient to promote a personalized and targeted approach to therapy.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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