PHARMACOLOGICAL THERAPY FOR HEART FAILURE
FROM EVIDENCE TO PRACTICE

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INTRODUCTION
About 30 years passed since the publication of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), which showed for the first time that the primary outcome of patients with heart failure (HF) can be improved by pharmacologic interventions [1]. In the last 3 decades, a plethora of large clinical trials [1-18] on use of pharmacological therapy and devices have resulted in an increasing use of evidences based therapy of heart failure (Table1). Despite these advances the morbidity and mortality of those afflicted with heart failure continues to remain high. Adherence to guidelines results in improved outcomes of heart failure patients.

Definition of heart failure (HF)
HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [19].

CALCIFICATION OF HEART FAILURE
Heart failure may be either predominantly systolic or diastolic failure. Systolic heart failure or heart failure with reduced EF (HF-rEF) are those patients with an EF<40%. Diastolic heart failure or HF with ‘preserved’ EF (HF-pEF) are those patients with symptoms and signs of heart failure but with entirely normal EF≥50%. Patients with an EF in the range 40–49% represent a ‘grey area’ and most probably have primarily mild systolic dysfunction and called heart failure with mid-range EF (HF-mrEF) (Table2) [19]. Differentiation of patients with HF based on LVEF is important due to different underlying etiologies, demographics, co-morbidities and response to therapies. It is estimated that 40 to 50 per cent of patients with heart failure have preserved systolic function or a relatively normal left ventricular ejection fraction [20]. HF-pEF seems to have a different epidemiological and etiological profile from HF-rEF. Patients with HF-pEF are older, more often female and obese than those with HF-rEF. They are less likely to have coronary heart disease and more likely to have hypertension and atrial fibrillation [21].

Treatments recommended in all symptomatic patients with HF WITH reduced ejection fraction (HFrEF)
In general, the goal of pharmacotherapy in HF is the improvement of the survival rate and the reduction of morbidity such as recurrent hospitalizations and symptoms while improving functional capacity and quality of life. Contemporary treatment options for patients with HFrEF should generally include a triple-therapy approach consisting of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II type I receptor blockers (ARBs) if ACEI are not tolerated, a beta-blocker (BB) and a mineralocorticoid-aldosterone receptor antagonist (MRA). This combination, which interacts with multiple neurohormonal pathways, has proven to reduce mortality and improve survival in multiple landmark trials (Table 1) and is thus recommended for all patients with HFrEF regardless of etiology.

Angiotensin-converting enzyme inhibitors ACEIs
There is clear-cut and compelling evidence that all patients with heart failure should receive ACE inhibitor therapy. Multiple well designed prospective randomized placebo-controlled trials, particularly CONSENSUS I, V-HEFT II and SOLVD [4-6] showed improvement in symptoms and survival in patients with mild to severe heart failure. ACEIs should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of the renin-angiotensin-aldosterone system (RAAS) & the target doses used in clinical trials (Table 3). There is evidence that in clinical practice the majority of patients receive suboptimal doses of ACEI.

ACEIs are also recommended in patients with asymptomatic LV systolic dysfunction to reduce the risk of HF development, HF hospitalization and death.
Renal function and serum potassium levels are assessed within 1-2 week and periodically thereafter. The adverse effects of these agents are dry cough, hypotension, worsening renal function, hyperkalaemia and angioedema.
Angiotensin receptor blockers (ARBs)
ARBs are recommended in patients with HF-rEF with current or prior symptoms who are ACE inhibitor intolerant, to reduce morbidity and mortality. The combination of ACEI/ARB for HFrEF was reviewed by the European Medicines Agency (EMA), which suggested that benefits

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are thought to outweigh risks only in a select group of patients with HFrEF in whom other treatments are unsuitable. Therefore, the combination of ACEI/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.

**Beta-blockers**

The beneficial role of B-blockers in the treatment of heart failure is well established. Agents commonly used in clinical practice are Metoprolol succinate, Carvedilol, Bisoprolol and Nebivolol. Several large randomized placebo-controlled studies in patients with class II-IV heart failure in particular the MERIT-HF, COPERNICUS, CIBIS and COMET trials showed mortality and morbidity benefit with usage of B-blockers [7-10].

There is consensus that beta-blockers and ACEIs are complementary, and can be started together as soon as the diagnosis of HFrEF is made. There is no evidence favouring the initiation of treatment with a beta-blocker before an ACEI has been started [10]. Beta-blockers should be initiated in clinically stable patients at a low dose and gradually up-titrated to the maximum tolerated dose (Table 3). In patients admitted due to acute HF (AHF) beta-blockers should be cautiously initiated in hospital, once the patient is stabilized. Beta-blockers are recommended in patients with a history of myocardial infarction and asymptomatic LV systolic dysfunction to reduce the risk of death [11].

Mineralocorticoid receptor antagonists (MRA), formerly aldosterone antagonists

Regulation of aldosterone synthesis is regulated by angiotensin-II and by plasma potassium. Activation of the mineralocorticoid receptor, which can also be activated by glucocorticoids, leads to several effects that can worsen cardiac function.

After the Randomized Aldactone Evaluation Study (RALES) [15] and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) [16], MRA therapy for patients with HFrEF and severe symptoms (NYHA class III and IV) has been established and implemented in the guidelines. In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial Zan nad et al. [17] showed that patients with HFrEF and milder symptoms (NYHA class II) might benefit from a therapy with a MRA in addition to the recommended and established drug therapy. The composite endpoint (cardiovascular mortality and hospitalization for HF) was significant lower (37%) in the eplerenone group in comparison to the placebo group. Furthermore, all-cause mortality (24%), cardiovascular death (24%), all-cause hospitalizations (23%), and HF hospitalizations (42%) were all significantly reduced. The results of the EMPHASIS-HF trial have led to the recommendation that all patients with reduced left ventricular function (LVEF ≤35%) and persisting symptoms (NYHA class II-IV) despite therapy with an ACEI (alternatively ARB) and a beta-blocker should receive a MRA unless there are contraindications.

The most important adverse effect of a therapy with MRA is hyperkalaemia. Therefore, caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium levels ≥5.0 mmol/L. Regular checks of serum potassium levels and renal function should be performed according to clinical status.

**Angiotensin receptor-neprilysin inhibitor (ARNI)**

A new drug class has recently emerged in HF therapy. ARNI is a novel treatment concept in HF. The first and to this date only substance in this class is "LCZ696," which is comprised of an ARB (valsartan) and sacubitril, a neutral endopeptidase (NEP, neprilysin) inhibitor. Neprilysin plays a crucial role in the degradation of natriuretic peptides. The therapeutic concept of the ARNI is based on the established inhibition of the renin-angiotensin-aldosterone system (RAAS) and an increase in endogenous natriuretic peptides by blocking their degradation by neprilysin. Inhibition of neprilysin counteracts the neurohumoral activation, which leads to vasoconstriction, sodium retention, and cardiac remodeling, increasing the RAAS-blocking effects [21]. The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial was a large randomized phase III study to investigate the beneficial effects of this new therapeutic concept [22]. A total of 8,442 HFrEF patients were enrolled in an ambulatory setting. Important inclusion criteria were: symptomatic HF (NYHA class II-IV), reduced left ventricular function (LVEF ≤40%, changed to ≤35% during the course of the study), and an estimated glomerular filtration rate ≥ 30 ml/min/1.73 m2). Therapy with sacubitril/valsartan (target dose: 400 mg/day, equivalent to 320 mg valsartan+80 mg sacubitril) was compared to a therapy with the ACEI enalapril (target dose: 20 mg/day). The primary endpoint, composed of cardiovascular mortality and HF hospitalizations, was significantly reduced in the sacubitril/valsartan group (20%). Furthermore, significant reduction was shown for cardiovascular mortality (20%), all-cause mortality (16%), and HF hospitalization (21%). Due to the distinct effects, therapy with sacubitril/valsartan is actually recommended in the current guidelines for all patients who meet the inclusion criteria and who remain symptomatic despite therapy with an ACEI (or ARB), a beta-blocker, and a MRA. When changing from an ACEI to sacubitril/valsartan, intake of the ACEI has to be stopped at least 36 hours before the first intake of sacubitril/valsartan in order to prevent angioedema. In regard to safety, the significantly higher incidence of symptomatic hypotension under therapy with sacubitril/valsartan is important to note. Thus, patients with very low blood pressure during ACEI treatment should not be switched to ARNI [23]. Regarding sacubitril/valsartan treatment in patients with diabetes mellitus, a recent subgroup analysis found a superiority of sacubitril/valsartan compared with enalapril independent from the patient's glycemic status (normoglycemic, pre-diabetes, diabetes) [24]. If-channel inhibitor

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MRA and ivabradine have become standard in symptomatic patients with HFpEF. The ARNI sacubitril/valsartan is a promising new addition to current pharmacological treatments. The results of the PARADIGM-HF trial have been so pronounced that they have led to a class IB recommendation by the ESC for symptomatic patients despite the ‘classic’ HF medication. Figure 1

REFERENCES


[18] Ponikowski P, Voors AA, Anker SD, Bueno H, Cland JG, Coats AJS et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:991–975


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