Pharmacology & Therapeutics 166 (2016) 136–149

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: H. Bönisch

# Pharmacology of heart failure: From basic science to novel therapies

Achim Lother [a,b,*], Lutz Hein [a,c,**]

[a] Institute of Experimental and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[b] Heart Center, Department of Cardiology and Angiology I, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[c] BIOSS Centre for Biological Signaling Studies, University of Freiburg, Freiburg, Germany

ARTICLE INFO

Available online 25 July 2016

*Keywords:*
Heart failure
Ivabradine
Angiotensin receptor and neprilysin inhibitor
Mineralocorticoid receptor
Omecamtiv mecarbil
Epigenetics

ABSTRACT

Chronic heart failure is one of the leading causes for hospitalization in the United States and Europe, and is accompanied by high mortality. Current pharmacological therapy of chronic heart failure with reduced ejection fraction is largely based on compounds that inhibit the detrimental action of the adrenergic and the renin–angiotensin–aldosterone systems on the heart. More than one decade after spironolactone, two novel therapeutic principles have been added to the very recently released guidelines on heart failure therapy: the HCN-channel inhibitor ivabradine and the combined angiotensin and neprilysin inhibitor valsartan/sacubitril. New compounds that are in phase II or III clinical evaluation include novel non-steroidal mineralocorticoid receptor antagonists, guanylate cyclase activators or myosine activators. A variety of novel candidate targets have been identified and the availability of gene transfer has just begun to accelerate translation from basic science to clinical application.

This review provides an overview of current pharmacology and pharmacotherapy in chronic heart failure at three stages: the updated clinical guidelines of the American Heart Association and the European Society of Cardiology, new drugs which are in clinical development, and finally innovative drug targets and their mechanisms in heart failure which are emerging from preclinical studies will be discussed.

© 2016 Elsevier Inc. All rights reserved.

## 1. Introduction

### 1.1. Epidemiology and pathophysiology of heart failure

Heart failure is one the most urgent medical issues of our time as it is associated with high mortality, morbidity and healthcare expenses. The prevalence of heart failure in the United States and Europe reaches up to 12% (Roger, 2013). The 5-year mortality of heart failure patients is estimated at 50% (Roger, 2013). The rising prevalence of heart failure has several reasons. First, heart failure is a syndrome that follows other cardiovascular diseases such as coronary artery disease, hypertension or valvular heart disease. Although survival after acute coronary syndrome has dramatically improved during the past decades, nevertheless myocardial damage that has occurred may cause heart failure in these patients. Second, mortality rate among heart failure patients is slowly declining for a few years now leading to increased prevalence (Roger, 2013). Third, heart failure is clearly associated with higher age (Roger, 2013), possibly due to a higher prevalence of comorbidities and risk factors.

Heart failure is a clinical diagnosis that is associated with the typical symptoms of dyspnea, orthopnea and edema. Heart failure with reduced ejection fraction (HFrEF) can be differentiated from heart failure with preserved ejection fraction (HFpEF), where predominantly diastolic filling of the ventricle is impaired (Ponikowski et al., 2016; Yancy et al., 2016). The key response to depressed left ventricular function is an activation of the adrenergic and the renin–angiotensin–aldosterone systems. While these help to maintain cardiac output and blood pressure by enhancing ventricular contractility and vasoconstriction in acute heart failure, continuing neuroendocrine activation drives maladaptive cardiac remodeling. Remodeling of the failing heart is characterized by cell death, inflammation and interstitial fibrosis, myocyte hypertrophy, altered calcium handling and activation of

*Abbreviations:* ACE, angiotensin-converting enzyme; ANP, atrial natriuretic peptide; ARNI, angiotensin receptor and neprilysin inhibitor; BNP, B-type natriuretic peptide; CamKII, calcium-calmodulin kinase II; cGMP, cyclic guanosine monophosphate; GRK, G protein-coupled receptor-kinase; HCN-channel, hyperpolarization-activated cyclic nucleotide-gated channel; HDAC, histone deacetylase; Il-1β, interleukin 1β; MR, mineralocorticoid receptor; MRA, mineralocorticoid receptor antagonist; NO, nitric oxide; NPR-A, natriuretic peptide receptor A; NYHA, New York Heart Association; PKA, protein kinase A; RKIP, Raf kinase inhibitor protein; SERCA2a, sarcoplasmic–endoplasmic reticulum ATPase 2a; sGC, soluble guanylate cyclase; SR, sarcoplasmic reticulum; TNFα, tumor necrosis factor α.

* Correspondence to: A. Lother, Heart Center, Department of Cardiology and Angiology I, Faculty of Medicine, University of Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany. Fax: +49 761 203 5318.
** Correspondence to: L. Hein, Institute of Experimental and Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Freiburg, Albertstr. 25, 79104 Freiburg, Germany. Fax: +49 761 203 5318.
*E-mail addresses:* achim.lother@universitaets-herzzentrum.de (A. Lother), lutz.hein@pharmakol.uni-freiburg.de (L. Hein).

http://dx.doi.org/10.1016/j.pharmthera.2016.07.004
0163-7258/© 2016 Elsevier Inc. All rights reserved.

distinct signaling cascades and gene expression programs in cardiac cells (Burchfield et al., 2013; Heusch et al., 2014).

### 1.2. Contemporary pharmacological therapy of heart failure

The American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines on heart failure therapy have been updated very recently (Ponikowski et al., 2016; Yancy et al., 2016). Today's pharmacological therapy of chronic HFrEF is largely based on compounds that inhibit the detrimental action of the adrenergic and the renin–angiotensin–aldosterone systems on the heart (Fig. 1). Beta blockers (CIBIS-II, 1999; MERIT-HF, 1999; Packer et al., 2002) and angiotensin-converting enzyme (ACE) inhibitors (CONSENSUS, 1987; SOLVD, 1991) reduce mortality and are recommended for all patients with symptomatic HFrEF. In addition, ACE inhibitors prevent the onset of symptoms and are recommended for patients with asymptomatic left ventricular dysfunction (SOLVD, 1992). Patients that do not tolerate ACE inhibitors should be treated with angiotensin receptor antagonists (Granger et al., 2003; Pfeffer et al., 2003). Mineralocorticoid receptor antagonists reduce all-cause mortality of patients with mild or moderate to severe HFrEF by 24% or 30%, respectively (Pitt et al., 1999; Zannad et al., 2011) (Fig. 1).

The $I_f$-channel inhibitor ivabradine (Swedberg et al., 2010) has been included in the ESC guidelines since 2012 and has now been added to the AHA guidelines. Ivabradine should be considered in patients with symptomatic HFrEF and a heart rate of ≥70 beats per minute under optimal therapy including a beta blocker (see Section 2) (Ponikowski et al., 2016; Yancy et al., 2016). The latest guideline updates also include the combined angiotensin receptor and neprilysin inhibitor (ARNI), valsartan and sacubitril (see Section 4.1, Fig. 1) (Ponikowski et al., 2016; Yancy et al., 2016).

In contrast to the remarkable advances in the therapy of HFrEF, options for patients presenting with HFpEF are still dreadful. Trials on beta blockers, ACE inhibitors or MR antagonists provided no or inconsistent evidence for an effect on mortality in HFpEF (Ponikowski et al., 2016). Comorbidities should be treated as possible to improve outcome.

In the following article, we review substances that have recently been added to treatment guidelines in detail and provide an overview on recent pharmacological developments for heart failure therapy from basic science towards clinical trials.

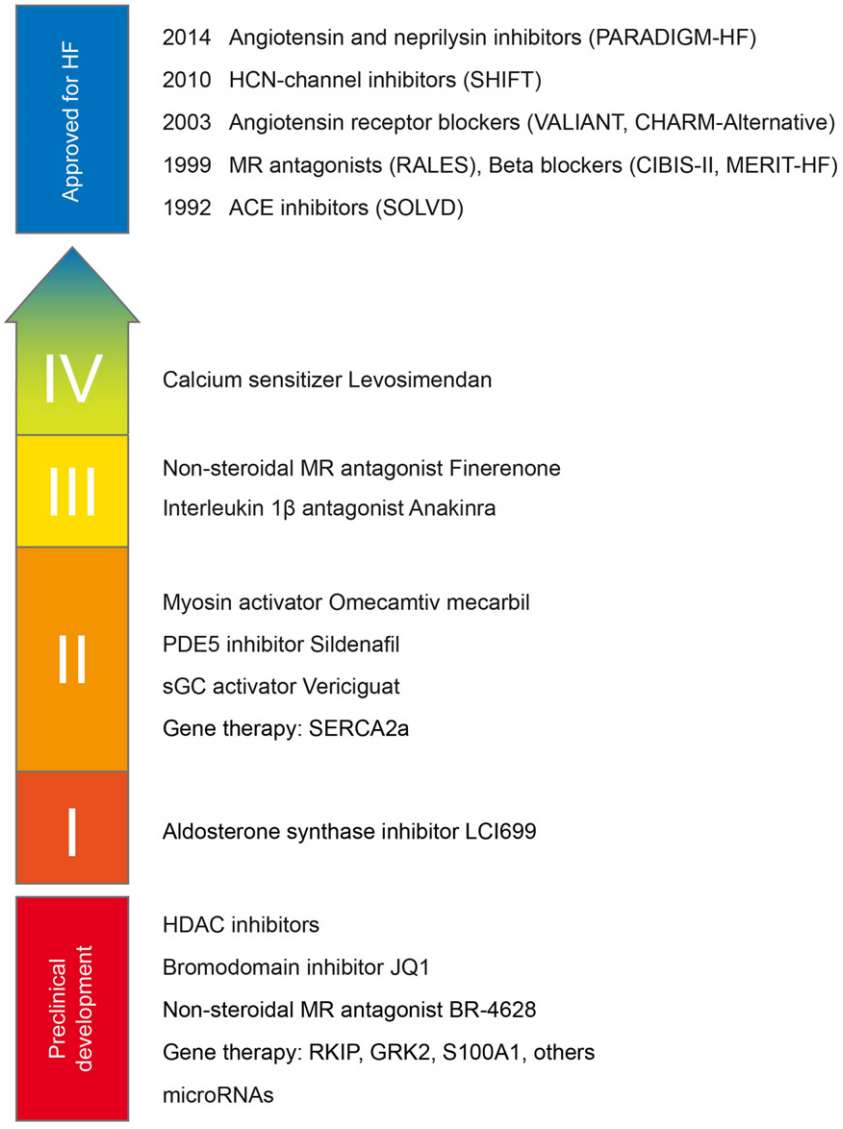


**Fig. 1.** Overview of current pharmacology and pharmacotherapy in chronic heart failure including approved drugs with years of respective landmark trials, new drugs that are in clinical trial development and innovative drug targets from preclinical, experimental studies. For references, see text.

Download English Version:

https://daneshyari.com/en/article/5557788

Download Persian Version:

https://daneshyari.com/article/5557788

Daneshyari.com