Handbook of Experimental Pharmacology 243

Johann Bauersachs
Javed Butler
Peter Sandner *Editors*

Heart Failure

Springer

Handbook of Experimental Pharmacology

Volume 243

More information about this series at http://www.springer.com/series/164

Johann Bauersachs • Javed Butler
Peter Sandner
Editors

Heart Failure

Springer

Editors
Johann Bauersachs
Klinik für Kardiologie und Angiologie
Medizinische Hochschule Hannover
Hannover, Niedersachsen
Germany

Javed Butler
Heart Institute
Stony Brook University
Stony Brook, New York
USA

Peter Sandner
Bayer Aktiengesellschaft
Drug Discovery – Cardiovascular Research
Heart and Vascular Diseases
Wuppertal, Nordrhein Westfalen
Germany

ISSN 0171-2004 ISSN 1865-0325 (electronic)
Handbook of Experimental Pharmacology
ISBN 978-3-319-59658-7 ISBN 978-3-319-59659-4 (eBook)
DOI 10.1007/978-3-319-59659-4

Library of Congress Control Number: 2017942786

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Heart Failure and Heart Failure Drug Therapy: Preface

Chronic heart failure (HF) remains a worsening global problem and represents the end sequelae of a variety of cardiovascular (CV) diseases. With the worldwide aging of the population and an increasing burden of comorbidities, it is projected that the increasing prevalence of HF will pose an even greater challenge to future healthcare systems than at present. Thus, identifying effective pharmacologic therapies for patients with HF, to reduce the burden of disease and to develop effective preventive strategies, is a call to action for researchers, for the pharmaceutical industry, and health care providers and systems across the world.

HF is broadly categorized as HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF), with approximately equal proportions of patients in each category. Morbidity and mortality in patients with HFrEF have improved in recent decades through modulation of the renin–angiotensin–aldosterone system (RAAS), β-adrenergic blockade, use of mineralocorticoid receptor antagonists (MRA), and most recently neprilysin inhibition (Packer et al. 2014). Despite these advances, there remains a significant residual risk of further hospitalization and death in patients with HFrEF. Importantly, no clinical trials to date have been successful in demonstrating improved outcomes for patients with HFpEF, and thus no therapies are approved for these patients. Similarly, no specific therapies exist for patients with worsening HF who are hospitalized. Comorbidities play a major role in determining outcomes in patients with HF. Recent data on the use of sodium/glucose cotransporter-2 inhibitors in patients with diabetes mellitus, and effects on CV outcomes, especially HF, have raised new possibilities for management of comorbidities in these patients (Zinman et al. 2015).

The focus of this volume of the Handbook of Experimental Pharmacology on HF is to review and highlight the pharmacologic advances made in HF research and to discuss promising targets for future treatments. Besides signaling pathways and pharmacological targets, this handbook will also cover epidemiology and comorbidities, clinical trial design, biomarkers, and current guideline-based therapy, allowing a complete overview of chronic HF. Given the high incidence and prevalence of HF, and the high morbidity and mortality associated with this disease, continuing intensive research and development efforts are essential to address the

unmet needs of these patients. This book, authored by outstanding experts in the field, will summarize existing knowledge and will also describe future treatment approaches, with the hope that this will stimulate further research, ultimately leading to new, effective therapies and improved outcomes in patients with HF.

Hannover, Germany — Johann Bauersachs
Stony Brook, NY, USA — Javed Butler
Wuppertal, Germany — Peter Sandner

References

Packer M, Desai AS, Gong J et al (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371(11):993–1004

Zinman B, Wanner C, Lachin JM et al (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373(22):2117–2128

Contents

The Three-Decade Long Journey in Heart Failure Drug Development

Kelly S. Lewis, Javed Butler, Johann Bauersachs, and Peter Sandner

Contents

Abstract

Heart failure is a global disease with increasing prevalence due to an aging worldwide population with increasing co-morbidities. Despite several therapeutic options available to treat HFrEF, morbidity and mortality remain high. Importantly, no approved therapies are available to treat HFpEF. This paper will briefly summarize the burden of disease, HF classification and definitions and the landmark clinical trials in both HFrEF and HFpEF. Given the increasing incidence and prevalence of HF and the high morbidity and mortality associated

K.S. Lewis (✉)
Department of Cardiology, Global Medical Affairs, Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA
e-mail: kelly.lewis@bayer.com

J. Butler
Department of Medicine, Division of Cardiovascular Medicine, Stony Brook University, Stony Brook, NY, USA

J. Bauersachs
Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany

P. Sandner
Department of Cardiology, Global Drug Discovery, Bayer Pharma AG, Wuppertal, Germany

J. Bauersachs et al. (eds.), *Heart Failure*,
Handbook of Experimental Pharmacology 243, DOI 10.1007/164_2016_101

with this disease, continued development efforts are essential to address the unmet needs of these patients.

Keywords
Heart failure • Heart failure statistics • Heart failure trials • HFpEF • HFrEF

1 Heart Failure: Disease, Definitions and Treatments

The importance of HF cannot be overemphasized due to its high prevalence, the severity of its clinical manifestations and related poor outcomes, and extraordinarily high societal costs. This paper will briefly summarize the burden of the disease, HF classification, guidelines, and the landmark HF trials to date, in both HFrEF and HFpEF.

2 The Global Burden of Heart Failure

Statistics related to HF are alarming: The global prevalence of HF is estimated to be about 26 million people, with more than one million hospitalizations annually in the USA and Europe (Ambrosy et al. 2014). In the USA alone, there were an estimated 5.7 million patients living with HF in 2012 (Writing Group et al. 2016), with this figure expected to increase by 46% from 2012 to 2030, resulting in more than eight million adults with HF (Writing Group et al. 2016; Heidenreich et al. 2013). In the countries represented by the European Society of Cardiology, there are 15 million patients living with HF (Dickstein et al. 2008; Ponikowski et al. 2014). The disease is more common with increasing age: in the USA, more than 80% of patients are 65 years of age or older (Bui et al. 2011) and the incidence of HF approaches 10 per 1000 population after 65 years of age (Lloyd-Jones et al. 2002). In countries such as Japan with aging populations, the number of patients with HF is predicted to increase considerably (Mosterd and Hoes 2007; Shiba and Shimokawa 2008). In Asia, the increased prevalence of HF has been attributed to the adoption of a Western lifestyle and its associated comorbidities (Sakata and Shimokawa 2013; Sasayama 2008). Additionally, with improved treatment of myocardial infarction and other CV diseases, those surviving CV events are at high risk of developing HF (Ambrosy et al. 2014). In economically developed countries, one in five people are expected to develop HF at some point in their lifetime (Lloyd-Jones et al. 2002).

Heart failure is the leading cause of hospitalization in elderly people in the USA and Europe, representing 1–2% of all hospitalizations (Blecker et al. 2013; Zannad et al. 2009; Braunwald 2013; Centers for Disease Control and Prevention 2016). In 2012, the total cost of HF in the USA was estimated to be approximately $40 billion, of which 68% was attributable to direct medical costs; these costs are expected to more than double by 2030 (Heidenreich et al. 2013).

Despite advances in therapy and management, HF remains a deadly disease. Across the globe, 17–45% of patients admitted to the hospital with HF die within 1 year of admission and the majority die within 5 years of admission. In-hospital mortality ranges from 2 to 17% (Maggioni et al. 2013). Survival rates are better for those treated in outpatient clinics, who typically have less severe symptoms than those in the hospital setting (Maggioni et al. 2013; Yancy et al. 2006). Approximately 50% of patients diagnosed with HF will die within 5 years (Go et al. 2013), a statistic worse than for bowel, breast, or prostate cancer (Brenner et al. 2012; Coleman et al. 2011; Siegel et al. 2012).

3 Definitions and Classifications

Several guidelines for the management and treatment of HF have been written in recent years by the European Society of Cardiology (ESC), as well as by the American Heart Association (AHA)/American College of Cardiology (ACC) (Ponikowski et al. 2016; Writing Committee et al. 2013; Yancy et al. 2016). These guidelines define HF as a "'clinical syndrome characterized by typical symptoms (e.g., shortness of breath, ankle swelling, and fatigue) and signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in decreased cardiac output and/or elevated intra-cardiac pressures at rest or with stress (Ponikowski et al. 2016; Writing Committee et al. 2013; Yancy et al. 2016)."

Generally the left ventricular ejection fraction (LVEF) determines how HF is categorized, which treatments are given, and what the prognosis may be. Ejection fraction (EF) is considered important in the classification of patients with HF because of differing patient demographics, comorbid conditions, prognoses, and response to therapies, and because most clinical trials selected patients based on EF (Fonarow et al. 2007). Until recently, guidelines for the management of HF divided patients with HF into two categories: those with reduced ejection fraction (EF $\leq$40%; HFrEF) and those with preserved ejection fraction (>40%; HFpEF) (Writing Committee et al. 2013). In the present ESC and AHA guidelines, HFrEF is defined as the clinical diagnosis of HF and LVEF $\leq$40% (Ponikowski et al. 2016; Yancy et al. 2016). Patients with HFpEF may not have entirely normal contractility but also do not have a major reduction in systolic function, and therefore the term "preserved ejection fraction" has been used. HFpEF has traditionally been defined as LVEF >40%, although it has been classified as EF from >40% to $\geq$55% across study types and by hospitalization status. Clinical studies of patients with HFpEF tended to use thresholds of 40–45%, while community-based studies and registries used more variable thresholds (Vaduganathan et al. 2016). Patients with HFpEF are usually older women with a history of hypertension, and share a similar comorbidity profile with patients with HFrEF (Adams et al. 2005). Hypertension is the most important cause of HFpEF, with a prevalence of 60–89% in patients with HFpEF (Sanderson 2007). Associated CV risk factors such as obesity, coronary artery disease (CAD), diabetes mellitus, atrial fibrillation (AF), chronic kidney disease,

Table 1 ESC and AHA guideline definitions of heart failure

Type of HF	HFrEF	HFmrEF	HFpEF
ESC criteria (Ponikowski et al. 2016)	• LVEF <40% • Symptoms ± signs	• LVEF 40–49% • Symptoms ± signs • Elevated levels of natriuretic peptides; BNP >35 or NT-proBNP ≥125 • Relevant structural heart disease (LVH and/or LAE) or diastolic dysfunction	• LVEF ≥50% • Symptoms ± signs • Elevated levels of natriuretic peptides; BNP >35 or NT-proBNP ≥125 • Relevant structural heart disease (LVH and/or LAE) or diastolic dysfunction
AHA/ ACCFCriteria (Writing Committee et al. 2013)	• LVEF ≤40%	• 41–49%[a]	• LVEF ≥50%

ACC American College of Cardiology, *AHA* American Heart Association, *BNP* B-type Natriuretic Peptide, *ESC* European Society of Cardiology, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *LAE* left atrial enlargement, *LVEF* left ventricular ejection fraction, *LVH* left ventricular hypertrophy, *NT-proBNP* N-terminal-pro-B-type Natriuretic Peptide
[a]ACC/AHA distinguishes LVEF 41–49% as "HFpEF, borderline (or intermediate)"

and hyperlipidemia are also highly prevalent in patients with HFpEF (Adams et al. 2005; Sanderson 2007).

Recently, the ESC guidelines added a new definition and third class of HF, described as HFmrEF (LVEF 41–49%) (Table 1). The ACC/AHA guidelines call this group borderline (or intermediate) (Writing Committee et al. 2013). Classifying HFmrEF as a separate entity may stimulate research into the underlying characteristics, pathophysiology, and treatment of this group of patients. HF with recovered or improved EF (HFiEF) has recently been proposed as a further new category (Ponikowski et al. 2016; Yancy et al. 2016). In the valsartan Heart Failure Trial (Val-HeFT), of those patients who had a baseline LVEF of < 35% and a follow-up echocardiographic assessment of EF at 12 months, 9.1% had a 12-month EF that improved to >40%. Recovery of the EF to >40% was associated with better survival than persistently reduced EF (Florea et al. 2016). Classifying HFmrEF and HFiEF as separate entities may stimulate research into the underlying characteristics, pathophysiology, and treatment of these patients and further distinguish whether they are a distinct clinical entity.

4 Historical Aspects Treatment Guidelines and Pivotal Trials in HFrEF

Until the 1980s, treatment for HFrEF was limited to digoxin and diuretics. Although effective for symptoms, there was no evidence of mortality benefits with this treatment regimen, and it was an inadequate option for many patients

with advanced symptoms. The evolution of treatment over the past 30 years has been extensive, beginning with the introduction of vasodilator therapy (hydralazine/isosorbide dinitrate combination) in 1986 and culminating in 2015 with the approvals in the USA of ivabradine and LCZ696 (valsartan/sacubitril), an angiotensin-receptor blocker/neprilysin inhibitor combination that reduced CV morbidity and mortality in the PARADIGM-HF trial (Packer et al. 2014). Key trials of therapies for HFrEF and HFpEF are depicted in Figs. 1 and 2.

The main goals of HF treatment are to reduce symptoms, prolong survival, improve quality of life, and prevent disease progression. Before the Veterans Administration Cooperative trial, the first outcomes trial in CV disease in the late 1960s, clinicians based their practice on prior experience, tradition, or observational studies. Prior to 1980, during the "non-pharmacologic era," treatments focused on lifestyle changes such as bed rest, reduced activity, and fluid restriction.

The 1980s marked the beginning of the "pharmacologic era," heralded by the first Vasodilator Heart Failure Trial (V-HeFT) (Cohn et al. 1986). Data from this trial suggested that the combination of hydralazine and isosorbide dinitrate, given in addition to diuretics and digoxin, had a favorable effect on left ventricular function, exercise capacity, and clinical outcomes in patients with HF. The two Vasodilator Heart Failure Trials, V-HFT-I and V-HFT-II were among the first large randomized, placebo controlled trials in CV medicine (Cole et al. 2011). The subsequent V-HeFT-II trial was undertaken to compare isosorbide dinitrate/

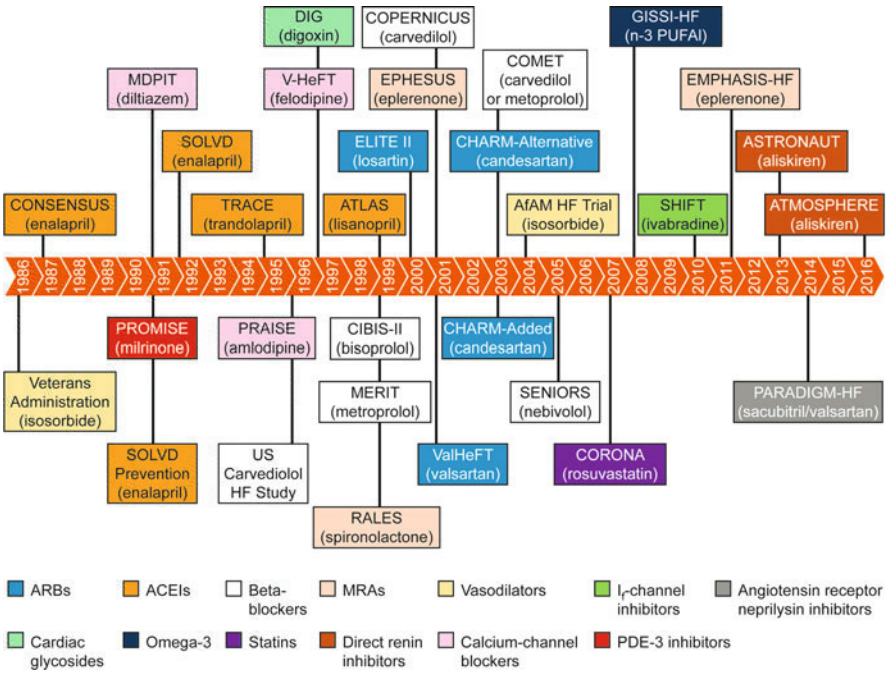

Fig. 1 30 years of development efforts in heart failure: Pivotal HFrEF trials

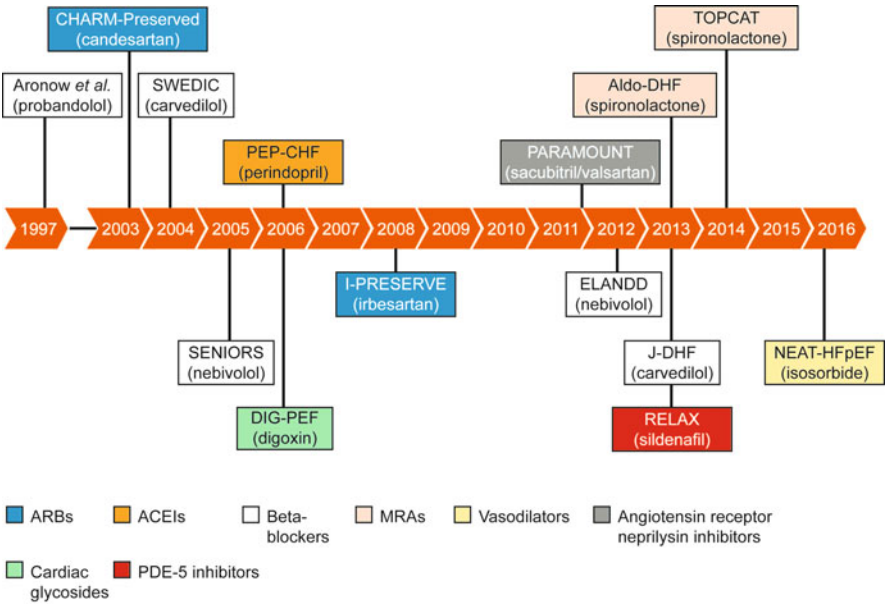

Fig. 2 30 years of development efforts in heart failure: Pivotal HFpEF trials

hydralazine with the angiotensin-converting enzyme (ACE) inhibitor, enalapril, and showed that enalapril conferred a survival benefit over isosorbide dinitrate/hydralazine (Cohn et al. 1991). A post hoc subgroup analysis suggested improved survival with isosorbide dinitrate/hydralazine among black patients (Carson et al. 1999), prompting the subsequently positive A-HeFT trial. The study was terminated early, owing to significantly higher mortality in the placebo group than in the isosorbide dinitrate/hydralazine group (Taylor et al. 2004).

The 1990s was a decade that brought neuro-hormonal interventions to the forefront of treatment pathways. Targeting the renal–angiotensin–aldosterone system (RAAS) provided evidence that ACE inhibitors, angiotensin II-receptor blockers (ARBs), and MRAs alter the natural history of heart failure.

There is considerable evidence to support the use of ACE inhibitors in symptomatic and asymptomatic patients with HFrEF and an EF of <40% (Ponikowski et al. 2016; Writing Committee et al. 2013; Yancy et al. 2016). Randomized trials have shown that therapy with ACE inhibitors leads to symptomatic improvement, reduced hospitalization, and enhanced survival in patients with HFrEF (Cohn et al. 1991; Cleland et al. 1985; Sharpe et al. 1984; Pfeffer et al. 1992; The SOLVD Investigators 1991; The CONSENSUS Trial Study Group 1987; Erhardt et al. 1995). ARBs were developed with the rationale that angiotensin II production continues in the presence of ACE inhibition, and are associated with a lower incidence of cough and angioedema than ACE inhibitors. In trials, long-term therapy with ARBs has been shown to reduce morbidity and mortality, especially in patients who are intolerant to ACE inhibitors (Cohn and Tognoni 2001; Pfeffer

et al. 2003a; Konstam et al. 2009; Pfeffer et al. 2003b). As such, guidelines recommend that initial therapy for patients with symptomatic HFrEF should comprise an ACE inhibitor or an ARB, along with β-blockers and an MRA, unless these drugs are contraindicated or not tolerated (Ponikowski et al. 2016; Writing Committee et al. 2013; Yancy et al. 2016).

In the placebo-controlled Randomized Aldactone Evaluation Study (RALES), adding spironolactone to baseline therapy in patients with HFrEF and moderate-to-severe symptoms decreased mortality and the risk of hospitalization for CV events (Pitt et al. 1999). Spironolactone has anti-androgenic and progesterone-like effects, which may cause gynecomastia or impotence in men, and menstrual irregularities in women. To avoid these side effects, eplerenone was developed. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone reduced all-cause mortality and hospitalization for CV events in patients with myocardial infarction complicated by left ventricular systolic dysfunction and HF (Pitt et al. 2001). In the more recent EMPHASIS-HF study, eplerenone when added to standard therapy reduced mortality and hospitalization in patients with HFrEF (New York Heart Association [NYHA] class II) and mild symptoms (Zannad et al. 2011). Consequently, current guidelines recommend the use of an MRA in HFrEF. Recently finerenone, a non-steroidal MRA with a potentially more favorable cardiac-to-renal activity ratio, has shown benefit over eplerenone in a population of patients with HFrEF (Filippatos et al. 2016; Bauersachs et al. 2015).

In angiotensin receptor-neprilysin inhibition (ARNI) therapy, an ARB is combined with an inhibitor of neprilysin, an enzyme that degrades the natriuretic peptides, bradykinin and adrenomedullin, as well as other vasoactive peptides. In the PARADIGM-HF trial, the ARNI valsartan/sacubitril significantly reduced the composite endpoint of CV death or HF hospitalization by 20%, compared with enalapril, in symptomatic patients with HFrEF tolerating an adequate dose of either ACE inhibitor or ARB. A similar benefit was seen for both all-cause mortality and HF hospitalization (Packer et al. 2015). Sacubitril/valsartan should not be given in combination with an ACE inhibitor as this is associated with an increased risk of angioedema.

Treatment with β-blockers, in addition to ACE inhibitors and digoxin, reduces the risk of death and hospitalization in patients with HF. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study demonstrated that carvedilol reduced 12-month mortality in patients with severe HF by 38% and the relative risk of death or HF hospitalization by 33%. The favorable effects of carvedilol were apparent even in patients at highest risk (i.e., those with recent or recurrent cardiac decompensation or very depressed cardiac function), who had a 33% decrease in the combined risk of death or hospitalization for a CV reason (95% CI, 14% to 48%, $P=0.002$) and a 33% decrease in the combined risk of death or hospitalization for heart failure (95% CI, 13% to 49%, $P=0.002$) when treated with carvedilol (Packer et al. 2002). In the Carvedilol or Metoprolol European Trial (COMET) study, carvedilol (25 mg twice daily) was compared with immediate-release metoprolol tartrate (50 mg twice daily). Carvedilol was associated with an

all-cause mortality of 34%, compared with 40% for metoprolol (Poole-Wilson et al. 2003). Based on these results, short-acting metoprolol tartrate is not recommended for use in the treatment of HF. In the DIG trial, digoxin had no effect on overall mortality in patients receiving diuretics and ACE inhibitors, but it did reduce the overall number of hospitalizations and the combined outcome of death or hospitalization attributable to worsening HF (Digitalis Investigation 1997). As participants in the DIG trial were not systematically treated with β-blockers and MRAs, the results of the ongoing DIGIT HF study (EudraCT DIGIT-HF) comparing the effects of digoxin and placebo in patients with advanced HFrEF on current standard therapy will be of major interest.

Elevated resting heart rate is associated with increased CV morbidity and mortality (Pocock et al. 2006; Lechat et al. 2001), independently of other established CV risk factors. The beneficial effects of β-blockers in HF have been thought to be related in part to heart-rate lowering effects. Ivabradine acts by selective inhibition of the pacemaker I_f channel, which is responsible for the autonomic capacity of the sinoatrial node. I_f channels are up-regulated in atrial tissue of patients with HF. In the SHIFT (Systolic Heart failure treatment with the I (f) inhibitor ivabradine Trial) study, ivabradine significantly reduced the composite primary endpoint of CV death and hospitalization for worsening HF by 18%, driven mainly by a reduction in hospitalization and deaths attributable to HF. CV deaths and all-cause mortality were not significantly reduced with ivabradine (Swedberg et al. 2012).

5 HFpEF

Although many treatments have been tested in HFpEF, all have returned neutral or negative results in randomized clinical trials. Treating the underlying comorbidities is the current mainstay of therapy. Guidelines recommend diuretics to control water retention, and to relieve breathlessness and edema. It is also recommended that hypertension is optimally managed and myocardial ischemia is assessed and treated, and in patients with AF heart rate is controlled.

The nitric oxide (NO) pathway is a key regulator of many physiological processes, and modulates vascular tone and myocardial performance. Numerous lines of evidence indicate that abnormalities in NO–cyclic guanosine monophosphate (cGMP) signaling play a central role in limiting exercise capacity in patients with HF. In HFPEF, comorbidities contribute to a systemic inflammatory state, which induces oxidative stress in the coronary microvascular endothelium and reduced myocardial NO bioavailability (Paulus and Tschope 2013). In the NEAT-HF trial, isosorbide mononitrate did not improve daily activity level, 6 min walk distance, dyspnea, quality-of-life scores, or NT-proBNP levels in patients with HFpEF. Indeed, dose-dependent decreases in daily activity levels were seen with isosorbide mononitrate (Redfield et al. 2015). Another means of targeting the NO-cGMP pathway is via phosphodiesterase inhibition. However, in the RELAX trial, the use of sildenafil in patients with HFpEF did not result in any improvement in

exercise capacity or clinical status over 24 weeks of treatment (Redfield et al. 2013). Reduced NO levels in HF leads to a decrease in the stimulation of an important enzyme called soluble guanylate cyclase (sGC). A lack of sGC stimulation leads to reduced activity of the NO-sGC-cGMP pathway, causing coronary dysfunction and progressive myocardial damage (Greene et al. 2013). More recently, a novel class of drug has been discovered which modulates cGMP production by targeting and stimulating the sGC enzyme (Gheorghiade et al. 2013). These compounds, sGC stimulators, have a dual mechanism of action: they have the ability both to stimulate sGC directly and independently of NO, and also to increase its sensitivity, thus reactivating the vital cardiovascular NO–sGC–cGMP pathway, even in the presence of the low NO levels seen in patients with HF. These compounds are now being studied in HF to target this critical pathway. A phase III clinical study (VICTORIA) is ongoing to study the once daily sGC stimulator, vericiguat, on outcomes in patients with HFrEF.

Use of β-blockers and RAAS blockers in patients with HFpEF has not produced positive results; there is no evidence from randomized trials of a clinical benefit of ACE inhibitors or ARBs in patients with HFpEF (Yusuf et al. 2003; Massie et al. 2008; Cleland et al. 2006; McKelvie et al. 2010). In the CHARM-PRESERVED trial of candesartan versus placebo in addition to background therapy (except ARBs), CV death did not differ between groups, but fewer patients in the candesartan group were admitted to hospital for HF (Yusuf et al. 2003). In the PEP-CHF study, perindopril did not improve the composite of all-cause mortality and unplanned HF-related hospitalization at 1 year, but did improve exercise capacity and NYHA functional class (Cleland et al. 2006). In the I-PRESERVE trial, treatment with irbesartan did not reduce the risk of death or hospitalization for CV causes in patients with HFpEF, nor did it improve any of the secondary outcomes, including quality of life (Massie et al. 2008). Trials of β-blockers have failed to provide conclusive results in HFpEF. A small-scale trial with carvedilol suggested that long-term therapy could improve diastolic function, with prevention or partial reversal of progressive left ventricular dilatation (Capomolla et al. 2000). Analysis of data from the SENIORS trial reported that nebivolol had similar efficacy in preventing all-cause and CV death in a subgroup of patients with HFpEF compared with those with HFrEF (van Veldhuisen et al. 2009).

Some argue that the findings from the TOPCAT study were inconclusive rather than neutral. Although spironolactone failed to demonstrate a benefit for the primary endpoint of CV death, cardiac arrest, or hospitalization for HF (Pitt et al. 2014), the overall neutral results may have been related to stratification by enrollment criteria and regional variations. Patients enrolled on the basis of hospitalization criteria had a lower event rate than those enrolled on the basis of natriuretic peptide level. In a post hoc analysis, spironolactone significantly reduced the rates of CV death and hospitalization for HF in patients enrolled from the Americas but not in those enrolled from Russia or Georgia (Pfeffer et al. 2015).

As in HFrEF, optimal heart rate is becoming an important target in the management of HFpEF. An analysis of patients with HFpEF in the I-PRESERVE database showed that every 12.4 bpm increase in heart rate was associated with a 13%

increase in the risk of a composite of CV death or hospitalization for HF (Bohm et al. 2014). Preliminary and experimental results with ivabradine indicated potential for heart-rate reduction in HFpEF. Ivabradine is currently undergoing further phase 2 testing in HFpEF in the ongoing EDIFY trial (EudraCT 2012).

Taken together, optimal medical therapy in patients with HFrEF modifies the clinical course of the disease. When patients are treated according to current guidelines, annual mortality is much lower than previously. However, in many patients commonly prescribed drug regimens are inadequate and more effort is necessary to achieve optimal medical therapy at evidence-based target doses (Packer 2016).

6 Conclusion

Despite 30 years of clinical research in HF and the approval of many effective therapies for patients with HFrEF, rates of CV events including hospitalizations, emergency department and office visits, the need for acute interventions (e.g., intravenous diuretics), and even death remain unacceptably high. Morbidity and mortality in patients with HFpEF are similar to those in patients with HFrEF, and there are no approved therapies. Understanding the molecular pathophysiology of HFpEF might serve as a key to identifying new pharmacologic targets for this disease. Clearly, additional innovative and more effective therapies that target new pathways are needed in all patients with HF.

References

Adams KF Jr, Fonarow GC, Emerman CL et al (2005) Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 149(2):209–216

Ambrosy AP, Fonarow GC, Butler J et al (2014) The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 63(12):1123–1133

Bauersachs J, Jaisser F, Toto R (2015) Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. Hypertension 65(2):257–263

Blecker S, Paul M, Taksler G et al (2013) Heart failure-associated hospitalizations in the United States. J Am Coll Cardiol 61(12):1259–1267

Bohm M, Perez AC, Jhund PS et al (2014) Relationship between heart rate and mortality and morbidity in the irbesartan patients with heart failure and preserved systolic function trial (I-Preserve). Eur J Heart Fail 16(7):778–787

Braunwald E (2013) Heart failure. JACC Heart Fail 1(1):1–20

Brenner H, Bouvier AM, Foschi R et al (2012) Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EUROCARE study. Int J Cancer 131 (7):1649–1658

Bui AL, Horwich TB, Fonarow GC (2011) Epidemiology and risk profile of heart failure. Nat Rev Cardiol 8(1):30–41

Capomolla S, Febo O, Gnemmi M et al (2000) Beta-blockade therapy in chronic heart failure: diastolic function and mitral regurgitation improvement by carvedilol. Am Heart J 139 (4):596–608

Carson P, Ziesche S, Johnson G et al (1999) Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-heart failure trial study group. J Card Fail 5(3):178–187

Centers for Disease Control and Prevention (2016) Available at http://www.cdc.gov/nchs/ahcd. Accessed 17 June 2016

Cleland JG, Dargie HJ, Ball SG et al (1985) Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. British Heart J 54(3):305–312

Cleland JG, Tendera M, Adamus J et al (2006) The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 27(19):2338–2345

Cohn JN, Tognoni G (2001) A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 345(23):1667–1675

Cohn JN, Archibald DG, Ziesche S et al (1986) Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a veterans administration cooperative study. N Engl J Med 314(24):1547–1552

Cohn JN, Johnson G, Ziesche S et al (1991) A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 325(5):303–310

Cole RT, Kalogeropoulos AP, Georgiopoulou VV et al (2011) Hydralazine and isosorbide dinitrate in heart failure: historical perspective, mechanisms, and future directions. Circulation 123(21):2414–2422

Coleman MP, Forman D, Bryant H et al (2011) Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. The Lancet 377(9760):127–138

Dickstein K, Cohen-Solal A, Filippatos G et al (2008) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the european society of cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 10(10):933–989

Digitalis Investigation G (1997) The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 336(8):525–533

Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS trial study group (1987). N Engl J Med 316 (23):1429–1435.

Erhardt L, MacLean A, Ilgenfritz J et al (1995) Fosinopril attenuates clinical deterioration and improves exercise tolerance in patients with heart failure. Fosinopril Efficacy/Safety Trial (FEST) study group. Eur Heart J 16(12):1892–1899

EudraCT (2012) Effect of ivabradine versus placebo on cardiac function, exercise capacity, and neuroendocrine activation in patients with Chronic Heart Failure with preserved left ventricular ejection fraction an 8-month, randomised double-blind, placebo controlled, international, multicentre study

Filippatos G, Anker SD, Bohm M et al (2016) A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. Eur Heart J 37(27):2105–2114

Florea VG, Rector TS, Anand IS et al (2016) Heart failure with improved ejection fraction: clinical characteristics, correlates of recovery, and survival: results from the valsartan heart failure trial. Circ Heart Fail 9(7)

Fonarow GC, Stough WG, Abraham WT et al (2007) Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry. J Am Coll Cardiol 50(8):768–777

Gheorghiade M, Marti CN, Sabbah HN et al (2013) Soluble guanylate cyclase: a potential therapeutic target for heart failure. Heart Fail Rev 18(2):123–134

Go AS, Mozaffarian D, Roger VL et al (2013) Heart disease and stroke statistics – 2013 update: a report from the American heart association. Circulation 127(1):e6–e245

Greene SJ, Gheorghiade M, Borlaug BA et al (2013) The cGMP signaling pathway as a therapeutic target in heart failure with preserved ejection fraction. J Am Heart Assoc 2(6):e000536

Heidenreich PA, Albert NM, Allen LA et al (2013) Forecasting the impact of heart failure in the United States: a policy statement from the American heart association. Circ Heart Fail 6 (3):606–619

Konstam MA, Neaton JD, Dickstein K et al (2009) Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. The Lancet 374(9704):1840–1848

Lechat P, Hulot JS, Escolano S et al (2001) Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II trial. Circulation 103(10):1428–1433

Lloyd-Jones DM, Larson MG, Leip EP et al (2002) Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation 106(24):3068–3072

Maggioni AP, Dahlstrom U, Filippatos G et al (2013) EURObservational research programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 15(7):808–817

Massie BM, Carson PE, McMurray JJ et al (2008) Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 359(23):2456–2467

McKelvie RS, Komajda M, McMurray J et al (2010) Baseline plasma NT-proBNP and clinical characteristics: results from the irbesartan in heart failure with preserved ejection fraction trial. J Card Fail 16(2):128–134

Mosterd A, Hoes AW (2007) Clinical epidemiology of heart failure. Heart 93(9):1137–1146

1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 325(5):293–302

Packer M (2016) Heart failure's dark secret: does anyone really care about optimal medical therapy? Circulation 134(9):629–631

Packer M, Fowler MB, Roecker EB et al (2002) Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 106(17):2194–2199

Packer M, Desai AS, Gong J et al (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371(11):993–1004

Packer M, McMurray JJ, Desai AS et al (2015) Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation 131(1):54–61

Paulus WJ, Tschope C (2013) A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 62(4):263–271

Pfeffer MA, Braunwald E, Moye LA et al (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 327(10):669–677

Pfeffer MA, McMurray JJV, Velazquez EJ et al (2003a) Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 349 (20):1893–1906

Pfeffer MA, Swedberg K, Granger CB et al (2003b) Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 362 (9386):759–766

Pfeffer MA, Claggett B, Assmann SF et al (2015) Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. Circulation 131(1):34–42

Pitt B, Zannad F, Remme WJ et al (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. N Engl J Med 341(10):709–717

Pitt B, Williams G, Remme W et al (2001) The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. Eplerenone Post-AMI heart failure efficacy and survival study. Cardiovasc Drugs Ther/sponsored by the Int Soc Cardiovasc Pharmacother 15(1):79–87

Pitt B, Pfeffer MA, Assmann SF et al (2014) Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 370(15):1383–1392

Pocock SJ, Wang D, Pfeffer MA et al (2006) Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 27(1):65–75

Ponikowski P, Anker SD, AlHabib KF et al (2014) Heart failure: preventing disease and death worldwide. ESC Heart Fail 1:4–25, http://www.escardio.org/static_file/Escardio/Subspecialty/HFA/WHFA-whitepaper-15-May-14.pdf

Ponikowski P, Voors AA, Anker SD et al (2016) 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 Heart J 37 (27):2129–2200

Poole-Wilson PA, Swedberg K, Cleland JG et al (2003) Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the carvedilol or metoprolol European trial (COMET): randomised controlled trial. Lancet 362(9377):7–13

Redfield MM, Chen HH, Borlaug BA et al (2013) Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. Jama 309(12):1268–1277

Redfield MM, Anstrom KJ, Levine JA et al (2015) Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med 373(24):2314–2324

Sakata Y, Shimokawa H (2013) Epidemiology of heart failure in Asia. Circ J official J Japn Circ Soc 77(9):2209–2217

Sanderson JE (2007) Heart failure with a normal ejection fraction. Heart 93(2):155–158

Sasayama S (2008) Heart disease in Asia. Circulation 118(25):2669–2671

Sharpe DN, Murphy J, Coxon R et al (1984) Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. Circulation 70(2):271–278

Shiba N, Shimokawa H (2008) Chronic heart failure in Japan: implications of the CHART studies. Vasc Health Risk manag 4(1):103–113

Siegel R, DeSantis C, Virgo K et al (2012) Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 62(4):220–241

Swedberg K, Komajda M, Bohm M et al (2012) Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine trial) study. J Am Coll Cardiol 59(22):1938–1945

Taylor AL, Ziesche S, Yancy C et al (2004) Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 351(20):2049–2057

Vaduganathan M, Michel A, Hall K et al (2016) Spectrum of epidemiological and clinical findings in patients with heart failure with preserved ejection fraction stratified by study design: a systematic review. Eur J Heart Fail 18(1):54–65

van Veldhuisen DJ, Cohen-Solal A, Bohm M et al (2009) Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). J Am Coll Cardiol 53(23):2150–2158

Writing Committee M, Yancy CW, Jessup M et al (2013) 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 128(16):e240–e327

Writing Group M, Mozaffarian D, EJ B et al (2016) Heart disease and stroke statistics-2016 update: a report from the American heart association. Circulation 133(4):e38–360

Yancy CW, Lopatin M, Stevenson LW et al (2006) Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 47(1):76–84

Yancy CW, Jessup M, Bozkurt B et al. (2016) 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for Heart Failure: an update of the 2013 ACCF/AHA guideline for the management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation

Yusuf S, Pfeffer MA, Swedberg K et al (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet 362(9386):777–781

Zannad F, Agrinier N, Alla F (2009) Heart failure burden and therapy. Europace 11(Suppl 5):v1–v9

Zannad F, McMurray JJ, Krum H et al (2011) Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 364(1):11–21

Zinman B, Wanner C, Lachin JM et al (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373(22):2117–2128

Epidemiology of Heart Failure

Francesco Orso, Gianna Fabbri, and Aldo Pietro Maggioni

Contents

Abstract

Heart failure (HF) is a major public health problem affecting more than 23 million patients worldwide. Incidence and prevalence rates vary significantly according to the source of data, but both increase with advancing age reaching, in the very elderly, prevalence rates that represent a challenge for the organization of medical care systems. Even if evidence-based treatments have improved

F. Orso
Department of Medicine and Geriatrics, Section of Geriatric Medicine and Cardiology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

ANMCO Research Center, Via La Marmora 34, 50121 Florence, Italy

G. Fabbri • A.P. Maggioni (✉)
ANMCO Research Center, Via La Marmora 34, 50121 Florence, Italy
e-mail: maggioni@anmco.it

J. Bauersachs et al. (eds.), *Heart Failure*,
Handbook of Experimental Pharmacology 243, DOI 10.1007/164_2016_74

prognosis in some patients with HF, patients with HF still need to be carefully characterized, described, and treated. Hospitalizations for acute HF are frequent and costly accounting for the vast majority of HF-related costs.

Keywords
Epidemiology • Heart failure • Prognosis • Registries

1 Introduction

Heart failure (HF) is a major clinical and public health problem with a prevalence of more than 23 million worldwide, associated with significant mortality, morbidity, and health-care expenditures; direct costs of HF account for almost ~2% of the total health-care budget in many European countries. Significant changes have occurred in the outcomes of patients with HF in the past 20 years mainly due to the development of pharmacological and non-pharmacological treatments that have improved survival in at least a group of patients with HF, specifically those with reduced ejection fraction (EF). Understanding the evolving epidemiology of HF is important in order to target interventions and for health-care planning.

In this chapter HF epidemiology will be discussed from two different and complementary approaches: the first part will describe general epidemiological data of the HF syndrome (e.g., incidence, prevalence, etiology, and outcomes), whereas in the second part, a picture of current cardiology clinical management of HF will be carried out by describing characteristics of patients with HF included in large European registries in patients with HF: the Italian Registry on Heart Failure Outcome (IN-HF Outcome; Tavazzi et al. 2013) and the Heart Failure Registry of the European Society of Cardiology (ESC-EORP-HF Pilot and Long Term) Maggioni et al. 2010; Maggioni et al. 2013a, b).

2 Incidence and Prevalence

In the past decades, the prevalence of HF has grown, particularly in the elderly, and the expression HF epidemic is frequently used to describe this phenomenon. This epidemic is the result of several factors, some of which may be related to the increased incidence (e.g., demographic changes with longer life expectancy in the general population or improved survival in patients with ischemic heart disease) and other to the increased survival due to the use of drugs and devices tested in several successful randomized clinical trials (RCTs) conducted in the past 30 years and able to improve the outcomes of ambulatory patients. Studies report an incidence of HF of 1–4/1,000 person-years (Levy et al. 2002; Roger et al. 2004; McMurray and Stewart 2000; Zarrinkoub et al. 2013). The prevalence has increased over time due to improved survival after diagnosis of HF and aging of the population, accounting for 1–3% in the adult population in developed countries, rising to

more than 10% and 30% among people >70 and >85% years of age, respectively (Dunlay and Roger 2014; Mosterd and Hoes 2007). Estimation of the lifetime risk for the development of HF is important for population health planning. Projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in >8 million people ≥18 years of age with HF (Heidenreich et al. 2013). Data regarding incidence and prevalence of HF derives from several studies, the most important of which are reported in Table 1. Notably there are significant differences across studies which might have several explanations:

- Type of studies. It should be noted that epidemiological studies considered were of different nature, some being based on administrative data (Curtis et al. 2008; Yeung et al. 2012; Zarrinkoub et al. 2013; Maggioni et al. 2016) and some others on clinical data derived from population-based observational studies (Levy et al. 2002; Roger et al. 2004; McCullough et al. 2002; Bleumink et al. 2004; Gottdiener et al. 2000).
- Different populations of HF patients. Some studies included patients with self-reported diagnosis of HF, others used hospital discharge diagnosis which could be administrative (ICD, International Classification of Diseases), with potential risk for up-coding of discharge diagnoses due to reimbursement incentives, or clinical.
- Different definitions and different diagnostic criteria of HF, which have changed significantly in the past years, have been used for the diagnosis of HF in these studies. Some studies used guideline diagnostic criteria, whereas others used Gothenburg, Boston, or Framingham diagnostic criteria (Eriksson et al. 1987; Carlson et al. 1985; McKee et al. 1971).

3 Hospitalizations and Mortality

Acute heart failure (AHF) is a complex, heterogeneous, clinical syndrome, often life threatening and requiring hospitalization for urgent therapy (Rosamond et al. 2007; Gheorghiade et al. 2005).

Despite the relevant burden of this clinical condition, therapeutic developments have been scarce in the last couple of decades; for this reason patients with HF remain at substantial risk for recurrent acute exacerbations and death (Fonarow et al. 2005; Abraham et al. 2008; Rudiger et al. 2005). Further, local conditions leading to hospitalization of patients with HF, as well as their in-hospital care, may be hugely different in various countries and can change over time (Maggioni et al. 2013a, b).

In total, there are more than 1 million hospitalizations for HF each year in the USA (Blecker et al. 2013). Heart failure is the leading cause of hospitalization among Medicare beneficiaries in the USA. Patients hospitalized with HF have the highest 30-day readmission rate (~25%) of any diagnosis (Jencks 2009); over half of patients are readmitted within 1 year, and multiple readmissions are common (Chun et al. 2012; Dunlay et al. 2009a). Many of these readmissions are due to

Table 1 Incidence, prevalence, and mortality of heart failure (Modified from Roger 2013)

Population (years)	Type of study	Incidence	Prevalence	Mortality
NHANES (2012) (Mozaffarian et al. 2015)	Interview-based survey	–	2.2% (≥20 years)	–
Framingham Heart Study (1950–1999) (Levy et al. 2002)	Population-based observational study	≈5/1,000 person-years	–	At 1-year age adjusted 1950–1969 Men: 30% Women: 28% 1990–1999 Men: 28% Women: 24%
Olmsted County (1979–2000) (Roger et al. 2004)	Population-based observational study	≈3/1,000	–	At 1 year (75 years old) 1979–1984 Men: 30% Women: 20% 1996–2000 Men: 21% Women: 17%
REACH Study (1989–1999) (McCullough et al. 2002)	Population-based observational study	Women: 3.7–4.2/1,000 Men: 4.0–3.7/1,000	Women: 0.4%–1.4% Men: 0.4%–1.5%	Per year: 17%
The Rotterdam Study (1989–2000) (Bleumink et al. 2004)	Population-based observational study	Women: 12.5/1,000 person-years Men: 17.6/1,000 person-years	1998: 7%	At 1 year: 37%
Cardiovascular Health Study (1990–1996) (Gottdiener et al. 2000)	Population-based observational study	Nonblack: 19/1,000 person-years Black: 19/1,000 person-years Women: 15/1,000 person-years Men: 26/1,000 person-years	–	–

(continued)

Table 1 (continued)

Population (years)	Type of study	Incidence	Prevalence	Mortality
Medicare beneficiaries (1994; 2003) (Curtis et al. 2008)	Administrative database	1994: 32/1,000/ person-years 2003: 29/1,000 person-years	1994: 9% 2003: 12%	1-year risk adjusted 1994: 29% 2002: 28%
Ontario, Canada (1997–2007) (Yeung et al. 2012)	Administrative database	1997: 4.5/ 1,000 persons 2007: 3.1/ 1,000 persons	–	1-year risk adjusted 1997 Outpatients: 18% Inpatients: 36% 2007 Outpatients: 16% Inpatients: 34%
Sweden (1990–2007) (Zarrinkoub et al. 2013)	Administrative database	2010: 3.1/ 1,000 persons	Crude: 1.8% Adjusted for demographic: 2.2%	Women 3.2/1,000 person-years Men 3.0/1,000 person-years 5-year survival rate was 48%
ARNO (2008–2012) (Maggioni et al. 2016)	Administrative database	–	2.2	28% at 1 year

non-cardiovascular causes (Maggioni et al. 2016; Carson et al. 2015; Desai et al. 2014).

This vulnerability to a diversity of illnesses may explain why interventions to prevent them should be delivered by a multidisciplinary team. A multidisciplinary strategy of intervention has been demonstrated to be more likely to reduce readmissions, specifically in the HF clinical area (Hansen et al. 2011; Rich et al. 1995).

Furthermore, annual total direct medical costs for patients with HF are $21 billion and expected to increase to $53 billion by 2030 (Heidenreich et al. 2013), and hospitalizations account for up to three-quarters of those costs (Dunlay et al. 2011).

Numerous studies have consistently shown that mortality from HF has steadily declined in recent decades (Barasa et al. 2014; Levy et al. 2002; Chen et al. 2011; Yeung et al. 2012), largely reflecting the introduction of medications (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineral-ocorticoid receptor antagonists, beta-blockers, and more recently ARNI) and

devices (e.g., implantable defibrillators and biventricular PM) which improve survival in patients with HFrEF (Guidelines ESC 2016). Trends in mortality from the time of initial diagnosis of HF are summarized in Table 1. However, despite these improvements, HF remains associated with poor outcomes. After initial diagnosis of HF, the estimated survival is 72–75% at 1 year and 35–52% at 5 years (Barasa et al. 2014; Levy et al. 2002). Most studies have suggested that women have better survival than men after diagnosis, adjusting for age (Levy et al. 2002; Roger et al. 2004).

Only very few studies examined the cause of death in patients with HF. In Olmsted County, 43% of deaths were due to non-cardiovascular causes, and the proportion was higher in patients with HFpEF (Henkel et al. 2008). In TIME-HF study causes and modes of death were specifically analyzed in elderly patients with HF: cause of death was more often non-cardiovascular in HFpEF patients than in HFrEF patients (33% vs. 16%, $P < 0.05$), and cardiac mode of death were more frequent in HFrEF patients (75% vs. 56%, $P < 0.05$), mainly due to more sudden deaths (25% vs. 7%, $P < 0.05$) Rickenbacher et al. 2012).

4 Etiology of Heart Failure

Several studies have examined the contribution of risk factors to the development of HF (Dunlay et al. 2009b; Folsom et al. 2009; Levy et al. 1996; Loehr et al. 2010; He et al. 2001). Different factors that predispose to HF in the general population have been identified, and, among these, coronary artery disease, hypertension, hypercholesterolemia, diabetes, smoking, arrhythmias, and obesity are the most important. These risk factors may coexist and interact with each other in an individual patient; nevertheless, their contribution to the development of HF varies significantly according to the type of HF. Patients with HFpEF are more frequently obese, with a history of hypertension and arrhythmias (particularly atrial fibrillation), whereas patients with HFrEF have more frequently a history of coronary artery disease, diabetes, and smoking (Senni et al. 2014). On the contrary, in the Physicians' Health Study, healthy lifestyle factors (normal weight, not smoking, regular exercise, moderate alcohol intake, consumption of breakfast cereals, and consumption of fruits and vegetables) were related to lower risk of HF (Djoussé et al. 2009).

Interesting and under intensive study is the role of chronic comorbidities that are frequent, particularly in the elderly (Saczynski et al. 2013), and have strong prognostic implications not only by summing their independent prognostic burden but also by limiting the use of evidence-based treatments and conditioning the eligibility for advanced heart failure therapies. Patients with HF are also affected by five or more concomitant chronic conditions in more than 50% of cases (Wong et al. 2011). Particular attention deserves noncardiac comorbidities that are highly prevalent in older patients with HF and strongly associated with adverse clinical