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The evolution of heart failure with reduced ejection fraction pharmacotherapy: What do we have and where are we going?

Ahmed Selim, Ronald Zolty, Yiannis S. Chatzizisis *

Division of Cardiovascular Medicine, University of Nebraska Medical Center, Omaha, NE, USA

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ABSTRACT

Cardiovascular diseases represent a leading cause of mortality and increased healthcare expenditure worldwide. Heart failure, which simply describes an inability of the heart to meet the body's needs, is the end point for many other cardiovascular conditions. The last three decades have witnessed significant efforts aiming at the discovery of treatments to improve the survival and quality of life of patients with heart failure; many were successful, while others failed. Given that most of the successes in treating heart failure were achieved in patients with reduced left ventricular ejection fraction (HFrEF), we constructed this review to look at the recent evolution of HFrEF pharmacotherapy. We also explore some of the ongoing clinical trials for new drugs, and investigate potential treatment targets and pathways that might play a role in treating HFrEF in the future.

Contents

1. Introduction

Heart failure affects 5.7 million adults in the United States (Mozzafarian, Benjamin, & Go, 2016). With close to 900,000 newly diagnosed adults every year, the number of HF patients is expected to exceed 8 million by 2030 (Mozaffarian, Benjamin, & Go, 2015). Despite the progress that was achieved over the last few decades in managing heart failure, the cost on the healthcare system continues to go up, with no significant change reported in the number of discharges for heart failure related overtime, which is estimated to cross one million discharges annually (Centers for Disease Control and Prevention, National Center for Health Statistics, 2010; Heidenreich et al., 2011). Heart failure is defined by the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines as "a complex clinical syndrome that results from any structural or functional impairment of

Abbreviations: ACC, American College of Cardiology; ACE, Angiotensin converting enzyme; ACEis, Angiotensin converting enzyme inhibitors; AHA, American Heart Association; AHF, Acute heart failure; ANP, Atrial natriuretic peptide; ARBs, Angiotensin receptor blockers; ARNIs, Angiotensin II receptor-neprilysin inhibitors; ATPase, Adenosine triphosphatase; AVP, Arginine-vasopressin; BBs, Beta blockers; BNP, Brain natriuretic peptide; cAMP, Cyclic AMP; CKD, Chronic kidney disease; CRF, Corticotropin-releasing factor; CV, Cardiovascular; EF, Ejection fraction; ET-1, Endothelin-1; FDA, Food and Drug Administration; GC-A, Guanylyl cyclase receptors subtype A; HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction; LV, Left ventricle; LVAD, Left ventricular assist device; MRAs, Mineralocorticoid receptor antagonists; NPs, Natriuretic peptides; NTG, Nitroglycerine; NYHA, New York Heart Association; OM, Omecamtive mecarbil; PCWP, Pulmonary capillary wedge pressure; PDE5, Phosphodiesterase-5; RAAS, Renin-angiotensin-aldosterone system; RCT, Randomized controlled trial; RyR2, Ryanodine receptors-2; SERCA, Sarcoplasmic reticulum Ca^{++} ATPase-2; SR, Sarcoplasmic reticulum; TGF-β, Transforming growth factor-β; VRAs, Vasopressin receptor antagonists.

* Corresponding author at: Division of Cardiovascular Medicine, University of Nebraska Medical Center, 982265 Nebraska Medical Center, Omaha, NE 68198, USA.
E-mail address: ychatzizisis@icloud.com (Y.S. Chatzizisis).

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ventricular filling or ejection of blood" (Yancy et al., 2013). In terms of classification, there are multiple ways to describe the syndrome of HF based on the side affected (right vs. left ventricular failure), the etiology of heart disease (ischemic vs. non-ischemic HF), the left ventricular ejection fraction (reduced EF ≤ 40%, borderline EF = 41–49%, preserved EF ≥ 50%), and the acuity (compensated vs. decompensated HF). Heart failure with reduced ejection fraction (HFrEF) is the underlying diagnosis for about half of the patients with symptomatic HF (Bursi et al., 2006), and represents the subset of HF patients that showed improvement of outcomes over the last few decades thanks to the new pharmacotherapeutic and device interventions (Owan et al., 2006).

The improved survival of heart failure with reduced ejection fraction (HFrEF), along with the projected increase in its prevalence, require the development of new strategies and approaches to ensure a better quality of life for these patients, and to try to limit the cost of their care to an acceptable level. This review covers the important aspects of the currently used HFrEF medications, including their mechanisms of action, the impact on outcomes, the results of the landmark clinical trials that led to their approval, and the guideline recommendations for their use. The review also goes over new agents that can be used to treat HFrEF in the future, some of which are in clinical trials, some have a questionable risk-benefit profile that requires further evaluation, and some are still in the early preclinical phase of development.

2. Pathophysiology

Heart failure syndrome involves the activation of multiple neurohormonal pathways that act as defense mechanisms to compensate for the state of impaired tissue perfusion. The long term effects of this activation can negatively impact the cardiovascular system's structure and function. The sympathetic nervous system gets activated in response to the low blood pressure sensed by the carotid and aortic arch baroreceptors, and reacts by releasing neurotransmitters such as epinephrine and norepinephrine (McCorry, 2007). These neurotransmitters bind to β_1 and β_2 adrenoceptors in the different cardiac tissues, including cardiomyocytes, SA node and the conduction system. The stimulation of β receptors (predominantly β_1 in the heart tissues) by neurotransmitters leads to the activation of G-proteins, which activate adenylyl cyclase, which in turn convert ATP to cyclic AMP (cAMP). cAMP plays a pivotal role in activating protein kinase (PK-A); an enzyme that causes an increase in the cellular calcium level by phosphorylating the L-type calcium channels and the ryanodine receptors of the sarcoplasmic reticulum. The increased intracellular calcium positively affects both the inotropic and the chronotropic functions of the heart. PK-A also enhances the myocardial contractility by phosphorylating the myosin light chains (Schmitz, Boknik, Linck, & Müller, 1996). The short-term effects include higher heart rate, increased myocardial contractility, and peripheral vasoconstriction. The long term effects of chronic sympathetic hyperactivity are in the form of accelerated LV remodeling, life threatening arrhythmias, and worsening of myocardial function (Florea & Cohn, 2014).

The activation of the renin-angiotensin-aldosterone system (RAAS) is another mechanism used by the body in response to heart failure. Sympathetic hyperactivity and poor kidney perfusion in HF are the main triggers of the RAAS (Andrew, 2002; Cody, 1997). Similar to the sympathetic system, the RAAS plays a compensatory role in the early stages of HF, although its long-term effects on the cardiovascular system are detrimental. The cascade of the RAAS starts with the renin being secreted from the juxtaglomerular cells of the kidney to stimulate the conversion of angiotensinogen to angiotensin I, followed by the action of the angiotensin converting enzyme (ACE), which further converts angiotensin I to angiotensin II. Angiotensin II is the active form of the enzyme, which can directly stimulate the angiotensin receptors, and stimulate the release of aldosterone from the adrenal cortex. The activation of the RAAS leads to an increase in the cardiac workload as a result of salt and water retention, sympathetic activation, systemic vasoconstriction, oxidative stress and eventually cardiac remodeling in the form of myocardial hypertrophy and fibrosis (Pacurari, Kafoury, Tchounwou, Ndebele, 2014; Schrier & Abraham, 1999).

There is another compensatory mechanism that takes place via the release of a group of vasoactive peptides, including natriuretic peptides (NPs), adrenomedullin, substance P and Urodilatin. NPs are secreted by the myocardium in response to an increase in the intra-cardiac filling pressure and include the atrial natriuretic peptide (ANP), the brain natriuretic peptide (BNP), and the C-type natriuretic peptide which is predominantly secreted by the vascular endothelium (Davidson, Barr, & Struthers, 1996; De Bold, Bruneau, & Kuroski de Bold, 1996; Krishnaswami, 2008). NPs aim at reducing both the cardiac preload and afterload via multiple mechanisms, including vasodilation, diuresis, and natriuresis. ANP and BNP have other favorable functions in patients with HF, including their protective effect against cardiac hypertrophy caused by angiotensin II, their inhibitory effect on the RAAS, and the ability of BNP to suppress the cardiac sympathetic stimulation (Potter, Abbey-Hosch, & Dickey, 2006). At the cellular level, ANP and BNP are believed to have their effect via the stimulation of a subtype of guanylyl cyclase receptors, called subtype A (GC-A), that is present in the heart, kidneys and blood vessels, and leads to an increase in the intracellular cGMP (Drewett & Garbers, 1994). There are multiple mechanisms by which NPs get cleared from the system, including the degradation by specific extracellular proteases, the breakdown by neprilysin, and receptor mediated degradation (Potter, 2011).

One other component that contributes to the syndrome of heart failure is inflammation, which is evidenced by the elevation of C-reactive protein, as well as the elevation of cytokines like serum interleukin-6 (IL-6) and tumor necrosis factor-alpha in patients with HF (Vasan et al., 2003). Multiple mechanisms were hypothesized to explain the origin of the inflammatory process in HF, including immune system activation, myocardial tissue injury, and the sympathetic hyperactivity (Anker & von Haehling, 2004), although more work needs to be done in this area in order to fully understand this component of the HF syndrome.

The different mechanisms outlined here contribute to the development and progression of the syndrome of HF. However, it is important to understand that an impaired myocardial function, whether systolic or diastolic, is not equivalent to the clinical diagnosis of HF, which depends on a constellation of signs and symptoms that form the body of this syndrome. This distinction was highlighted in the ACC/AHA HF staging system (Table 1), which labelled patients with structural heart disease who have no symptoms as stage "B", while symptomatic patients were given stage "C" (structural heart disease with symptoms of HF) and "D" (advanced heart disease with severe HF symptoms). Patients with risk factors for developing HF who have never had symptoms or evidence of myocardial dysfunction were classified as stage "A" (Hunt et al., 2001).

3. Current HFrEF pharmacotherapeutic agents

3.1. Renin-angiotensin-aldosterone system (RAAS) inhibitors

3.1.1. Angiotensin converting enzyme inhibitors

ACE inhibitors (ACEis) were one of the earliest groups of medications to show mortality benefits in patients with HFrEF (Table 2).

Table 1
ACCF/AHA staging system for patients with heart failure.

ACCF/AHA stage of heart failure	Description
Stage A	Individuals with no functional or structural heart disease but are at high risk for the development of heart failure
Stage B	Patients with structural heart disorders but have no symptoms or signs of heart failure
Stage C	Patients with previous or current symptoms of heart failure in the setting of an underlying heart disease
Stage D	Patients with advanced heart failure that require hospital admission, advanced cardiac therapies or palliative therapy

Table 2
HFrEF pharmacotherapy in today's clinical practice.

Group/agents	Mechanism of action	Major trials	Outcomes	ACCF/AHA guidelines[a]	ESC guidelines[a]	References
Digoxin	Increases intracellular calcium by inhibiting the sodium-potassium ATPase pump	Dig	Digoxin reduces HF-hospitalization	Class IIa(B) for symptomatic HFrEF patients	Class IIb(B) for symptomatic HFrEF patients	The Digitalis Investigation Group (1997)
ACEi Enalapril Lisinopril Ramipril Captopril Perindopril Benazepril	Inhibit the conversion of angiotensin I to angiotensin II	CONSENSUS SOLVD ATLAS	ACEis reduce all-cause mortality and hospital admissions	Class I(A) for all patients with HFrEF	Class I(A) for patients with HFrEF	The CONSENSUS Trial Study Group (1987), The SOLVD Investigators (1992), Packer, Poole-Wilson, and Armstrong (1999)
ARBs Valsartan Candesartan Losartan Telmisartan Irbesartan Azilsartan Olmesartan	Inhibit angiotensin II from binding to angiotensin receptors	Val-HeFT CHARM-overall	ARBs reduce combined end-point of CV-mortality and hospital admission	Class I(A) for patients with HFrEF who are intolerant to ACEi	Class I(B) for symptomatic HFrEF patients who cannot tolerate ACEi	Cohn and Tognoni (2001), Pfeffer et al. (2003)
β-Blockers Carvedilol Bisoprolol Metoprolol	Selective or non-selective inhibition of beta receptors	US Carvedilol CIBIS II MERIT-HF COPERNICUS	BB reduce all-cause mortality and hospitalization	Class I(A) for all patients with HFrEF	Class I(A) for patients with HFrEF	Packer et al. (1996), CIBIS-II Investigators and Committees (1999), MERIT-HF study group (1999), Packer, Califf, et al. (2002), Packer Fowler, et al. (2002)
MRAs Spironolactone Eplerenone	Inhibit spironolactone at the receptor level	RALES EPHESUS EMPHASIS-HF	MRAs reduce all-cause mortality and CV-hospitalization	Class I(A) for patients with HF and EF ≤35%	Class I(A) for symptomatic patients with HFrEF despite being on ACEi and BB	Pitt et al. (1999, 2003), Zannad et al. (2010)
Hydralazine-dinitrate	Direct vasodilation (hydralazine), release of nitric oxide and activation of guanylyl cyclase (isosorbide dinitrate)	A-HEFT	Hydralazine-dinitrate reduce all-cause mortality, hospitalization for HF, and quality of life in AA	- Class I(A) for use in AA with symptomatic HFrEF. - Class IIa(B) for all patients with ACEi/ARB intolerance	- Class IIa(B) for symptomatic black patients with EF ≤ 35%, or EF < 45% with LV dilatation despite treatment with ACEi & BB. - Class IIb for all HFrEF patients how cannot tolerate ACEi/ARBs	Taylor, Ziesche, Yancy, Carson, and D'Agostino (2004)
VRAs Tolvaptan Conivaptan Lixivaptan	Inhibit AVP at the receptor level, promote free water loss, and correct hyponatremia	EVER-EST	VRAs improve body weight and symptoms in AHF	Class IIb(B) in AHF patients with severe persistent hyponatremia and at risk of developing cognitive symptoms	Tolvaptan can be used in patients with volume overload and resistant hyponatremia (no recommendation class given)	Gheorghiade, Abraham, et al. (2007), Gheorghiade, Konstam, et al. (2007)
Ivabradine	Block sinoatrial node funny channels (I_f)	SHIFT	Ivabradine reduce CV-death and hospitalization	Class IIa(B-R) for use in HFrEF patients with HR ≥ 70 despite being on maximal dose of BB	Class IIa(B) for symptomatic patients with EF ≤ 35% and HR ≥ 70 despite treatment with BB, and for those unable to tolerate or have contraindication to BB	Swedberg, Komajda, and Böhm (2012)
ARNI Sacubitril/valsartan	Sacubitril increases the level of intrinsic natriuretic peptides by inhibiting its degradation by neprilysin	PARADIGM-HF	ARNI reduce composite endpoint of CV-death or HF-hospitalization	Class I(B) for use in HFrEF patients who tolerate ACEi or ARB	Class I(B) as a replacement for ACEi in symptomatic HFrEF patients despite optimal treatment.	McMurray et al. (2014)
Inotropic agents (dopamine, dobutamine, PDE III inhibitors, epinephrine)	Multiple[a]	OPTIME-CHF ADHERE	Inotropic agents might increase mortality in patients with decompensated HFrEF	Class I(C) for use in cardiogenic shock. Class IIa(B) for use as a bridge to ACT or as palliative therapy	Class IIb(C) for use in hypotension/hypoperfusion despite adequate vascular filling. *Remark*: one additional agent, levosimendan, is included in the ESC guidelines)	Felker et al. (2003), Abraham et al. (2005)

AA = African American; ACCF = American College of Cardiology Foundation; ACEi = angiotensin converting enzyme inhibitors, ACT = advanced cardiac therapies; ARBs = angiotensin receptor blockers; AHA = American Heart Association; AHF = acute heart failure; ARNI = angiotensin II receptor-neprilysin inhibitors; AVP = arginine-vasopressin; BB = beta blockers; CV = cardiovascular; ESC = European Society of Cardiology; HF = heart failure, HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; MRAs = mineralocorticoid receptor antagonists; PDE = phosphodiesterase; VRA = vasopressin receptor antagonists.

[a] Recommendations are presented as class (level of evidence); refer to ACCF/AHA and ESC guidelines classes (Ponikowski et al., 2016; Yancy et al., 2013).

The CONSENSUS Trial Study Group (1987) and The SOLVD Investigators (1991, 1992) trials studied the effect of Enalapril on patients with reduced ejection fraction (<35%), and showed a significant decrease in the mortality and hospital admission for all NYHA functional classes of HF (The CONSENSUS Trial Study Group, 1987; The SOLVD Investigators, 1991, 1992). Subsequent randomized trials have demonstrated the role of ACEis in HFrEF following myocardial infarction using other members or the group, including Ramipril and Captopril (Pfeffer, 1993; The Acute Infarction Ramipril Efficacy, AIRE Study Investigators, 1993). Lisinopril was introduced in the ATLAS study (1999) (Packer et al., 1999), a randomized clinical trial that included over 3100 patients and was designed to investigate the benefit of ACEi dose titration. It showed that higher dose Lisinopril (32.5–35 mg daily) significantly reduces HF admissions and the combined end point of mortality and hospitalization for any cause compared to the lower dose group (2.5–5 mg daily) in HF patients with EF ≤ 30%, although there was no significant difference in mortality between the two groups.

The ACC/AHA/HFSA guidelines recommended the use of ACEi in patients with prior or current symptoms of chronic systolic HF (Class I, level of evidence A) with dose up-titration. The guidelines did not recommend the use of a specific ACE inhibitor over another (Yancy et al., 2016).

3.1.2. Angiotensin receptor blockers

Angiotensin receptor blockers (ARBs) are another group of medications that inhibit the RAAS by preventing angiotensin II from binding to the angiotensin II receptors (Fig. 1). One of the earlier trials in ARBs was the Val-HeFT, which included over 5000 HFrEF patients randomized to receive Valsartan versus placebo and showed a significant reduction in combined end point of mortality and morbidity in the treatment group (Cohn & Tognoni, 2001). The CHARM-Alternative was a double blind, placebo controlled trial that included over 2000 HFrEF who were ACEi-intolerant (Granger, McMurray, & Yusuf, 2003). CHARM-Alternative showed a reduction in cardiovascular death and hospital readmission in the treatment (Candesartan) group, but no reduction in all-cause mortality compared to placebo. The concept of double blockade by adding ARBs to ACEi was tested in CHARM-Added (Candesartan + ACEi of the physicians choice) and in ValHeFT (Valsartan vs. placebo, with patients divided into 4 subgroups based on their background medications: beta-blockers, ACEi, both, or neither) and showed no significant improvement in mortality, with a concern for hyperkalemia and renal impairment in those receiving ACEi in addition to ARB (Cohn & Tognoni, 2001; Granger et al., 2003; McMurray, Ostergren, & Swedberg, 2003). ARBs have the advantage of causing significantly lower incidence of cough compared to ACEi.

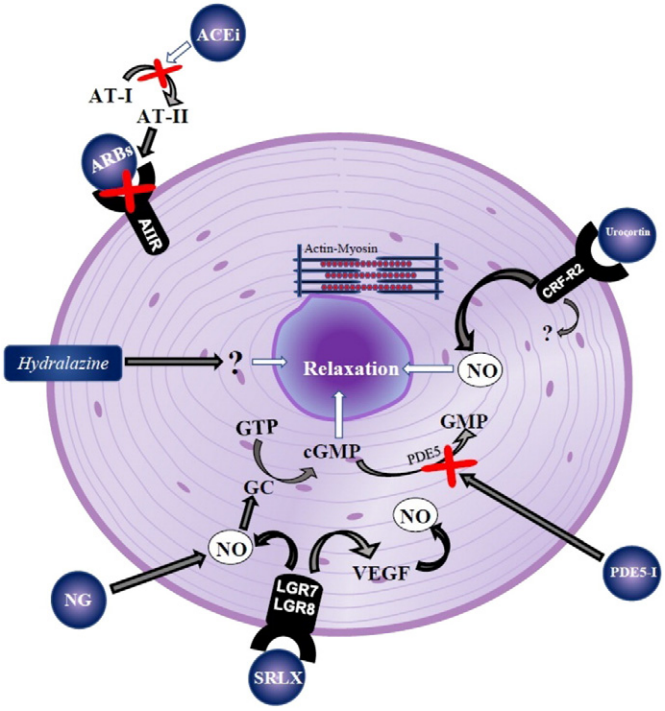

Fig. 1. Vasodilators in HF — mechanism of action of some vasodilators on the vascular smooth muscle cell. ACEi = angiotensin converting enzyme inhibitor; AIIR = angiotensin-II receptors; ARBs = angiotensin receptor blockers; AT-I = angiotensin-I; AT-II = angiotensin-II; cGMP = cyclic guanosine monophosphate; CRF-R2 = corticotropin releasing hormone receptor-2; GC = guanylyl cyclase; GMP = guanosine monophosphate; GTP = guanosine triphosphate; NG = nitroglycerin; PDE5 = phosphodiesterase-5; PDE5-I = phosphodiesterase-5 inhibitors; SRLX = serelaxin; VEGF = vascular endothelial growth factor.

Given that angiotensin II could be produced independent of ACE (Petrie, Padmanabhan, & McDonald, 2001), it was initially thought that ARBs might lead to superior outcomes in HF compared to ACEis due to their ability to perform a more efficient RAAS blockade, although multiple clinical trials, including the ELITE II study (Pitt et al., 2000), failed to prove such superiority. Current ACC/AHA/HFSA guidelines recommend the use of ARBs in HFrEF patients that are intolerant to ACEi (Class I, level of evidence A).

3.1.3. Mineralocorticoid receptor antagonists (MRAs)

MRAs are antagonists of spironolactone at the receptor level. In addition to their action as diuretics, MRAs are believed to help HFrEF patients by elevating the serum potassium level, and by antagonizing the deleterious effects of aldosterone on the cardiac muscle (Ovaert, Elliott, Bernay, Guillot, & Bardon, 2010). The RALES trial showed that spironolactone significantly decreases all-cause mortality and HF hospitalization in advanced HFrEF patients (EF ≤ 35%, NYHA Classes III & IV), and also improves NYHA functional class. The RALES trial showed that adding spironolactone to ACEi doesn't increase the risk of hyperkalemia or renal failure (Pitt et al., 1999). Eplerenone emerged as a more selective MRA that does not cause gynecomastia, a complication spironolactone is notorious for. EPHESUS was the first major randomized trial to investigate the use of MRAs in HFrEF (EF < 40%) post MI (Pitt et al., 2003). It showed that Eplerenone can decrease all-cause mortality, cardiovascular mortality and hospitalization in this patient population. EMPHASIS-HF is a more recent trial; it included older (>55 years) HFrEF patients with milder symptoms (EF ≤ 30%, or EF ≤ 35% in association with QRS > 130 ms, and NYHA Class II symptoms) and showed that Eplerenone decreases all-cause mortality, CV mortality, and hospitalization for HF (Zannad et al., 2010). The use of MRAs is recommended in HFrEF patients (EF ≤ 35%, NYHA II–IV) by the ACCF/AHA 2013 guidelines (Yancy et al., 2013).

3.2. Beta blockers

Beta-blockers (BBs) help patients with HF by counteracting the excessive sympathetic drive in order to limit its long term harmful effect on the heart. The first large-sized clinical trial to evaluate the effect of BB on HF was the US Carvedilol trial, which showed a reduction in all-cause mortality and cardiovascular hospitalization in patients with HFrEF (EF ≤ 35%) (Packer et al., 1996). CIBIS-II, MERIT-HF and COPERNICUS are three cornerstone trials that followed and showed similar improvement in HFrEF outcomes with the use of BBs (Bisoprolol, Metoprolol-XL and Carvedilol respectively) (CIBIS-II Investigators and Committees, 1999; MERIT-HF study group, 1999; Packer, Califf, et al., 2002). The COMET trial was designed to investigate potential differences in outcomes between two members of the BB family, and although carvedilol has shown lower all-cause mortality compared to metoprolol tartrate, the assumption of superiority could not be confirmed, given that the beta-blocking agent used in the MERIT-HF trial was metoprolol succinate, not tartrate (Poole-Wilson et al., 2003). The question regarding which agent to be started first in patients with HFrEF, ACEi vs. BB, was answered in the CIBIS-III trial, which showed

no difference in the survival and all-cause hospitalization between the two strategies (Willenheimer et al., 2005). The MOCHA trial showed a dose-related improvement in ejection fraction, survival, and hospitalization rate in patients receiving carvedilol, with the maximum dose (25 mg bid) associated with the best outcomes (Bristow et al., 1996).

The 2013 ACCF/AHA guidelines named three BBs (bisoprolol, carvedilol, and sustained release metoprolol succinate) as Class I medications for use in HFrEF with current or prior symptoms.

3.3. Hydralazine-isosorbide dinitrate combination

Hydralazine is a direct vasodilator that causes relaxation of the vascular smooth muscle by decreasing the intracellular calcium concentration (Ellershaw & Gurney, 2001), while the vasodilator effect of nitroglycerine is achieved via the release of nitric oxide (Fig. 1), which leads to the activation of guanylyl cyclase (Brandes, Kim, & Schmitz-Winnenthal, 2000). Both medications have an antihypertensive effect and can decrease the cardiac workload. The V-HEFT I study compared the use of an isosorbide dinitrate-hydralazine combination vs. prazosin vs. placebo in HFrEF, and showed a favorable effect on mortality and left ventricular function in those receiving the isosorbide dinitrate-hydralazine combination (Cohn et al., 1986).

The V-HEFT II study compared enalapril to the isosorbide dinitrate-hydralazine combination and failed to show a significant mortality difference between the two groups at the end of the follow up period (Cohn et al., 1991). A post-hoc analysis of the V-HEFT trial showed that only African Americans had mortality benefits from using hydralazine-nitrates (Carson, Ziesche, Johnson, & Cohn, 1999). This finding prompted the launching of the A-HEFT trial, which included 1050 HFrEF patients who identified themselves as African American and showed that the combination of isosorbide dinitrate and hydralazine causes an improvement in survival, hospitalization, and quality of life in this population (Taylor et al., 2004).

The combination of hydralazine and isosorbide dinitrate is recommended for use in African American patients with symptomatic HFrEF in addition to ACEi or ARBs (Class I, level of evidence A). It is also recommended for use in HFrEF patients regardless of their race in case of ACEi/ARBs intolerance (Class IIa, level of evidence B).

3.4. Inotropic agents

There are three main uses for inotropic agents in HFrEF; (i) hospitalized patients with low cardiac output and an evidence of end-organ dysfunction, (ii) patients being bridged pending more definitive form of therapy (i.e. ventricular assist devices or cardiac transplant), or (iii) palliative therapy for patients with end-stage HFrEF. The mechanism of action of inotropes and their side effects vary between different agents. For example, norepinephrine is a catecholamine that carries both α and β agonist properties, and is frequently used in patients with septic shock. Norepinephrine is also helpful in some cardiogenic shock patients with systemic vasodilation, a situation that is commonly seen post implantation of mechanical assist devices, although caution is needed when norepinephrine is used with cardiac patients as it increases heart rate, myocardial oxygen demand, and can lead to arrhythmias (Jolly et al., 2005).

Dobutamine is another catecholamine that stimulates β1 and β2 adrenoceptors, with predominant β1 activity. It is the agent of choice in many patients with cardiogenic shock due to its ability to decrease the cardiac afterload by causing systemic vasodilation in addition to enhancing the myocardial contractility (Overgaard & Dzavik, 2008). The use of dobutamine is associated with many side effects including hypotension, tachycardia, myocardial ischemia, arrhythmias and eosinophilic myocarditis. The long-term use of a continuous infusion of dobutamine was shown to increase in-hospital mortality and HF admissions (Wang, Zhu, & Shan, 2015).

Dopamine is an endogenous catecholamine that has a dose dependent effect on the cardiovascular system (Overgaard & Dzavik, 2008), with low doses (<3 μg/kg/min) causing renal and splanchnic vasodilation and intermediate doses (3–10 μg/kg/min) causing an increase in myocardial contractility, heart rate, and pulmonary capillary wedge pressure. An alpha-receptor mediated vasoconstriction with an increase in the systemic vascular resistance is the predominant effect at higher doses of dopamine (10 to 20 μg/kg/min). The use of lower doses of dopamine to improve renal function (the so-called renal dose) did not show any benefits and is not recommended (Bellomo, Chapman, Finfer, Hickling, & Myburgh, 2000), although the 2013 ACCF/AHA guidelines continued to list the use of low-dose dopamine to improve diuresis and preserve renal functions as IIb (level of evidence B).

Milrinone is a phosphodiesterase-3 inhibitor that has both inotropic and vasodilator effects. It is most commonly used in patients with end-stage heart failure (Colucci, Wright, Jaski, Fifer, & Braunwald, 1986). Unlike the previously discussed inotropic agents, milrinone can stimulate myocardial contractility independent of β-receptors, a property that makes it attractive for use in HF patients who are on beta blockers. Because milrinone leads to an increase in the cellular cyclic adenosine monophosphate (cAMP), it helps reduce the pulmonary artery pressure and helps patients with right ventricular dysfunction, which adds another advantage to its use in a certain subset of HFrEF patients. Milrinone can cause arrhythmias and hypotension and its use was also associated with increased mortality in multiple clinical trials (Abraham et al., 2005; Amsallem, Kasparian, Haddour, Boissel, & Nony, 2005; Felker et al., 2003). The use of milrinone should be restricted to patients with cardiogenic shock, patients with end-stage HF that are not candidates for advanced cardiac therapies (ACT), and as a bridging agent in HFrEF patients waiting to receive ACT.

Levosimendan is another non-catecholamine inotropic agent that works by increasing the sensitivity of the myocardial cells to calcium, without actually increasing the intracellular calcium concentration. Levosimendan also causes vasodilation via its effect on the potassium channels in the vascular smooth muscles, and also via inhibiting phosphodiesterase-3 enzyme (Papp et al., 2012). Levosimendan is approved for use in Europe, but not approved by FDA for use in the United States.

In the ACCF/AHA 2013 guidelines, the use of inotropes as a temporary measure to support the circulation in patients with cardiogenic shock is given Class I, their use as "bridge therapy" in end-stage HF patients planned to have more advanced intervention (i.e. assist device or cardiac transplant), and as palliation for end-stage HF patients who couldn't be stabilized with the other forms of medical therapy is given Class II, while the long-term use of inotropic agents in the absence of any of the specified indications is considered Class III (harmful).

3.5. Digoxin

Digoxin is one of the oldest medications used for heart failure. It is a cardiac glycoside that increases the intracellular calcium levels by inhibiting the sodium-potassium adenosine triphosphatase (ATPase) pump, and causing an increase in myocardial contractility (Smith, Antman, & Friedman, 1984). Digoxin was shown to reduce HF-hospitalization with no effect on mortality in the DIG trial (The Digitalis Investigation Group, 1997). It also has an important role in treating patients with HFrEF and atrial fibrillation, as it can help achieve rate control without negatively affecting contractility (Veldhuisen, Gelder, Ahmed, & Gheorghiade, 2013). The use of digoxin requires monitoring of serum digoxin levels, with a recommended therapeutic level of 0.5–0.8 ng/mL. Digoxin level ≥ 1.2 ng/mL was associated with increased mortality (Rathore, Curtis, Wang, Bristow, & Krumholz, 2003). The use of digoxin is given Class IIa indication in the 2013 ACC/AHA guideline for use in HFrEF patients to decrease hospitalizations.

3.6. Vasopressin receptor antagonists

Arginine-vasopressin (AVP), widely known as the antidiuretic hormone, is a polypeptide produced by the hypothalamus and is considered one of the main players in heart failure syndrome. AVP is secreted as a result of the RAAS activation when a hypoperfusion state is detected by the baroreceptors. By stimulating vasopressin receptors in the renal collecting tubules, AVP reduces the amount of free water excreted in an attempt to improve organ perfusion. It is an effect which leads to excess water retention, as well as being one of the potential mechanisms of hyponatremia in patients with advanced HF (Goldsmith, Francis, Cowley, Levine, & Cohn, 1983), which was shown to be associated with worse outcomes (Gheorghiade, Abraham, et al., 2007; Lee and Packer, 1986). Vasopressin receptor antagonists (VRA) were introduced as agents that can promote free water loss and correct hyponatremia. EVER-EST study included over 4000 symptomatic HFrEF patients and showed that Tolvaptan, a selective antagonist of the renal vasopressin receptors (V2 receptors), can improve body weight and symptoms in patients admitted for acute HF (Gheorghiade, Konstam, et al., 2007), without any effects on the long-term mortality or morbidity (Konstam et al., 2007).

Besides Tolvaptan, other selective (Lixivaptan), as well as nonselective (Conivaptan) vasopressin receptor antagonists have shown an increase in serum sodium levels without significant impact on outcomes in HFrEF (Abraham, Shamshirsaz, McFann, Oren, & Schrier, 2006; Russell, Adams, Shaw, Gattis, & O'Connor, 2003; Udelson et al., 2007). The use of VRAs, either selective or nonselective, was given a Class IIb recommendation in acute hospitalized HF patients with severe persistent hyponatremia that are at risk for developing cognitive symptoms based on the 2013 ACCF/AHA guidelines.

3.7. Intravenous vasodilators

3.7.1. Nitroglycerin

Nitroglycerin is one of the oldest pharmacotherapeutic agents used in cardiology; it was introduced in the mid-19th century as a treatment for patients with angina (Murrell, 1979). Nitroglycerin works by forming nitric oxide that stimulates guanylate cyclase, which accelerates the production of cyclic guanosine monophosphate (cGMP), a vascular smooth muscle relaxant, from guanosine triphosphate (GTP, Fig. 1) (Kukovetz, Holzmann, & Romanin, 1987). Because of its systemic vasodilatory effect, nitroglycerin can decrease both cardiac preload and afterload, and leads to a decrease in myocardial oxygen demand. The increase in cardiac output with the use of nitroglycerin seems to be proportionate to the left ventricular filling pressure, with a more significant increase in cardiac output reported in patients with elevated LV filling pressure at baseline (Cohen, Downey, & Sonnenblick, 1973; Miller, Vismara, & Williams, 1976). The vasodilatory effect of nitroglycerin on the coronary arteries seems to contribute to the improvement in cardiac output as well, especially in the presence of an underlying coronary artery disease (Malondzak, Green, & Sragg, 1970).

3.7.2. Sodium nitroprusside

Sodium nitroprusside is another vascular smooth muscle relaxant that works by producing nitric oxide via a different mechanism (Kowaluk, Seth, & Fung, 1992). The use of sodium nitroprusside was popular in hypertensive emergencies because of its rapid onset of action and short half-life, while the evidence of its use in acute coronary syndrome, with and without HF is conflicting (Cohn, Franciosca, & Francis, 1982; Durrer, Lie, & VanCapell, 1982). In heart failure, sodium nitroprusside showed an improvement in clinical and hemodynamic indices, with a significant decrease in systemic vascular resistance, increase in stroke volume and cardiac index. These findings were reported in multiple studies that included patients with refractory HF (Guiha, Cohn, Mikulic, Franciosa, & Limas, 1974; Lukes, Calixto, & Romero, 1979), with favorable response mainly achieved in patients with elevated systemic vascular resistance at baseline.

The use of intravenous nitroglycerin and sodium nitroprusside is listed as Class IIb in the 2013 ACCF/AHA guidelines as adjuvants to diuretic therapy for relief of symptoms in patients with acute decompensated HF.

4. Novel pharmacotherapeutic agents in practice

4.1. Ivabradine

Ivabradine is a first-in-class medication that aims at decreasing the heart rate by blocking the sinoatrial node's funny channels. The funny channels (I_f) are mixed sodium-potassium channels that play an essential role in enabling the sinoatrial (SA) node to generate its own spontaneous rhythm. Ivabradine has a unique ability to decrease the heart rate via its effect on the SA node without influencing the conduction system or the myocardial contractility. The benefit of using Ivabradine in HFrEF was shown in the SHIFT trial, with 6505 symptomatic HF patients with low EF (≤35%) and sinus rhythm ≥70 bpm randomized to receive Ivabradine or placebo. The starting dose was 5 mg twice daily (BID) up-titrated to 7.5 mg BID, with dose reduction allowed in patients who develop bradycardia (HR ≤ 60). Although all participant subjects were expected to be on guideline-directed BB dose as per the study protocol, only one fourth of the patients were on BB at target dose, and 11% were not on any beta-blocking agent.

The major adverse events reported in this study were symptomatic bradycardia (5%), visual symptoms (3%) and slightly higher, but statistically significant incidence of atrial fibrillation (9% in the treatment group vs. 8% in the placebo group) (Swedberg, Komajda, & Böhm, 2010). Ivabradine achieved a significant 18% reduction ($P < 0.0001$) in the primary composite endpoint of cardiovascular death and hospitalization compared to placebo, the effect of which was mainly driven by a reduction in HF death and hospitalization rather than all-cause mortality. In a subgroup analysis performed by the manufacturer, it was shown that Ivabradine's ability to improve HF mortality and admission is directly related to the reduction of HR regardless of the use BB or its dose (Swedberg et al., 2012).

Given the inability of Ivabradine to show any added all-cause mortality benefits in HFrEF, and the remarkable, well-studied mortality benefits of BB, it was stressed in the 2016 ACC/AHA/HFSA guidelines update that Ivabradine should only be used in HFrEF patients who are on maximal tolerated dose of BB with persistent HR ≥ 70 bpm (Class IIa, level of evidence B-R).

4.2. Angiotensin II receptor-neprilysin inhibitors (ARNIs)

Neprilysin inhibition was studied as a pathway that can potentially increase the levels of intrinsic NPs by slowing its clearance from the system (Fig. 2). But because neprilysin has a role in the breakdown of angiotensin II, its inhibition can lead to an increase in the angiotensin II levels, an effect that was detected with the use of Candoxatril in normal persons (Ando, Rahman, Butler, Senn, & Floras, 1995). Multiple neprilysin inhibitors were tested in patients with HF, including Ecadotril and Omapatrilat (also has ACE inhibiting properties), but didn't show any improvement in outcomes, with a concern for higher incidence of severe angioedema especially with Omapatrilat (Cleland & Swedberg, 2016; Packer, Fowler, et al., 2002). LCZ696 (the previously assigned name to the Sacubitril/Valsartan combination), is the first-in-class medication that has a dual action as a neprilysin inhibitor and angiotensin receptor antagonist. The neprilysin inhibitor part of the combination, Sacubitril, is a prodrug that gets enzymatically converted to the active form (Feng et al., 2012).

The PARADIGM-HF trial, described as the largest clinical trial in heart failure to date, compared the use of Sacubitril/Valsartan to Enalapril (10 mg twice daily) in 8442 HF patients with EF ≤ 40%, NYHA functional

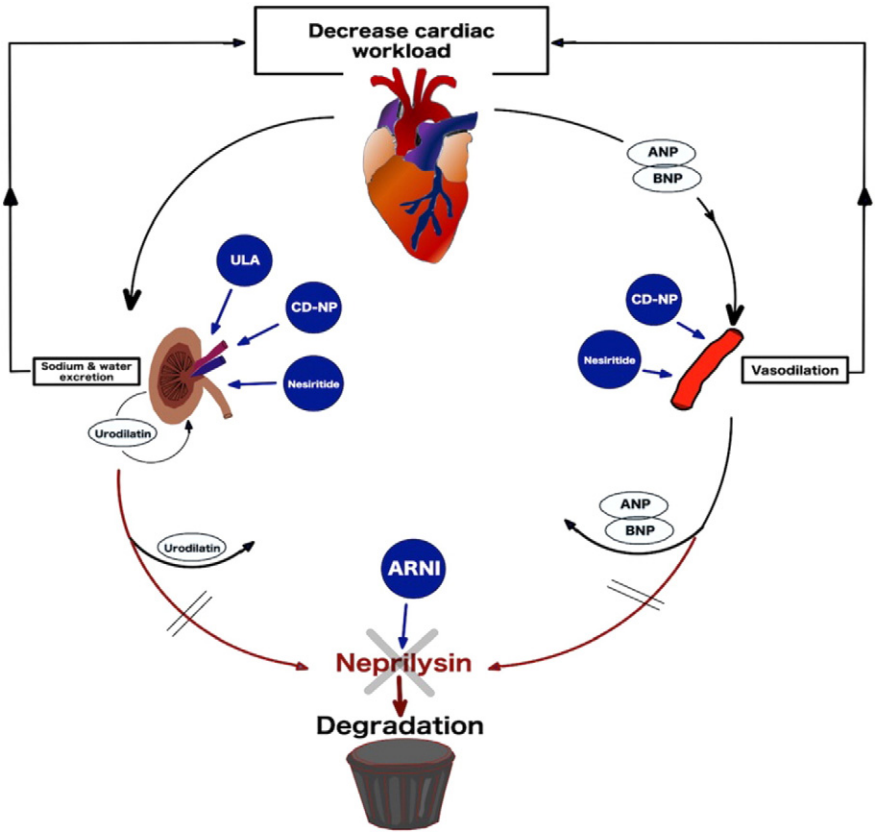

Fig. 2. Natriuretic peptides — natriuretic peptides that affect the cardiovascular system (both endogenous and synthetic). ANP = atrial natriuretic peptide; ARNI = angiotensin receptor blocker-neprilysin inhibitor; BNP = brain natriuretic peptide; CD-NP = synthetic chimeric peptide; ULA = ularitide.

Classes II–IV and elevated BNP/NT-proBNP. Subjects were on optimized background HF medications, including BB (93%) and MRA (60%). The trial was stopped early because of the significant reduction in cardiovascular death or HF hospitalization (the primary endpoint) by 20% compared to the Enalapril group (HR = 0.80, $P < 0.001$), and the reduction in cardiovascular death (HR = 0.80, $P < 0.001$) (McMurray et al., 2014). There was no statistically significant difference in the incidence of angioedema between the two treatment groups, and elevated serum potassium and creatinine were less in the Sacubitril/Valsartan, with no difference in the discontinuation of therapy due to hypotension between the two groups (although hypotension was reported more frequently with the Sacubitril/Valsartan group).

In the 2016 HF guidelines update, ARNI is recommended for use in HFrEF patients who tolerate ACEi or ARBs (Class I), with a "B" level of evidence based on the data obtained from this single randomized clinical trial (Yancy et al., 2016).

5. Novel agents in clinical trials

5.1. Serelaxin

Serelaxin is a recombinant version of human relaxin, a peptide hormone that gets secreted from the corpus luteum during pregnancy and causes pelvic relaxation (MacLennan, 1991). Relaxin has a potent vasodilator effect that was shown in both animal and human studies (Conrad, 2010), and it also causes an increase in the renal blood flow associated with an increase in the glomerular filtration rate (Conrad, 2004; Conrad, Gaber, & Lindheimer, 2009). The vasodilatory effect of relaxin resorted to an increase in the production of nitric oxide and vascular endothelial growth factor (VEGF), along with an inhibitory effect on angiotensin II and endothelin (Teichman et al., 2009). Relaxin binds to unique G-protein coupled receptors called LGR7 & LGR8 (Fig. 1), which were found in blood vessels and heart tissues (Hsu & Nakabayashi, 2002). The binding of relaxin to these receptors results in an activation of multiple mediators including mitogen-activated protein kinase and phosphatidylinositol-3-kinase, which in turn induces an increase in cAMP (Teichman et al., 2009). The mechanism by which relaxin causes a rapid dilation of vessels is believed to involve $G\alpha_{i/o}$ protein coupling to endothelial NO synthase, and protein kinase B (also known as Akt) (McGuane, Debrah, & Sautina, 2011).

Early clinical data were obtained from a study done in Germany that included 16 HF patients who received 24 hour infusion of relaxin (Dschietzig et al., 2009). The study showed trends toward an increase in cardiac index, a decrease in pulmonary wedge pressure, a decrease in NT-pro BNP, and improvement in the renal functions with relaxin. The Pre-RELAX-AHF is a phase II placebo-controlled (Table 3), multicenter study that included 234 patients admitted for acute heart failure with elevated BNP/NT pro BNP, mild to moderate renal impairment and systolic BP > 125 mm Hg. The study showed a significant improvement in dyspnea, with trends toward a decrease in 60-day cardiovascular and renal readmission rates, and cardiovascular death in patients who received serelaxin (Teerlink et al., 2009). The RELAX-AHF trial is a phase III, double-blind study that enrolled 1161 patients to receive 48 h of IV serelaxin (30 μg/kg/day) vs. placebo and showed a significant improvement of symptoms with decreased hospital length of stay and increased 180-day survival with no change in hospital readmission (Felker et al., 2014).

There was some skepticism about the results, given that HF medications with favorable effect on mortality usually decrease hospital admissions as well (Hjalmarson, Goldstein, & Fagerberg, 2000). There was also the inability to explain the mechanism by which a short term, 48-hour medication can improve long-term mortality outcomes (Cannon, McKean, Jhund, & What, 2015). Serelaxin could not obtain FDA approval for use in AHF to improve symptoms based on the results of RELAX-AHF.

Table 3
Novel HFrEF pharmacotherapeutic agents in clinical and pre-clinical trials.[a]

Group/agent	Mechanism of action	Available data	Current status	References
Empagliflozin	Selective inhibition of SGLT2 that leads to an increased urinary glucose excretion and osmotic diuresis.	Based on a post hoc analysis of the EMPA-REG OUTCOME, there is a reduction in cardiovascular death, HF hospitalization and all cause hospitalization in patients treated with empagliflozin compared to placebo	A clinical outcome trial is currently underway The ESC guidelines give empagliflozin class IIa(B) to prevent or delay onset of HF in diabetic patients	Carbone (2016)
Serelaxin	Vasodilation and increases GFR by increasing the production of NO and VEGF, inhibition of angiotensin II and endothelin	RELAX-AHF (phase III trial) showed improvement of symptoms with decreased hospital length of stay and increased 180-day survival.	RELAX-AHF-2 is underway to assess the 180-day mortality and worsening HF at 5 days.	Felker et al. (2014)
Omacamtive mecarbil (OM)	Accelerates the conversion of actin-myosin complex from a weakly bound to a strongly bound	- ATOMIC-AHF: dyspnea improvement - COSMIC-HF is a phase II: OM improves myocardial function.	Phase III clinical outcome trial is underway	Cleland, Teerlink, and Senior (2011), Teerlink et al. (2016)
SERCA2a activator	Increases SR calcium uptake	SERCA2a activator causes significant reduction of PCWP	SERCA-LVAD is evaluating the effect of SERCA2a activator on HF patients with LVAD	Periasamy, Bhupathy, and Babu (2008), Bers, Eisner, and Valdivia (2003), Jessup et al. (2011)
New MRAs	Inhibit cardiac hypertrophy and fibrosis, diuresis, decrease blood pressure.	Finerenone was non-inferior to spironolactone in decreasing NP levels in HF patients with CKD, with less incidence of hyperkalemia and worsening renal functions.	More clinical studies needed	Pitt, Kober, and Ponikowski (2013)
Aldosterone synthase inhibitors	Inhibit the enzymatic conversion of deoxycorticosterone to aldosterone	Aldosterone synthase inhibitor improved cardiac hemodynamic parameters, LV function, and prevented progressive LV remodeling in a rat model of HF	Data based on clinical studies in human needed	Mulder, Mellin, and Favre (2008)
CD-NP	A synthetic natriuretic peptide that causes diuresis, natriuresis, and vasodilation	CD-NP causes reduction in PCWP and increase in UOP along with drop in BP	More clinical studies needed	Lee, Chen, and Lisy (2009)
Urocortin-2	It is a corticotropin-releasing factor that has vasodilatory, anti-inflammatory, inotropic, and chronotropic effects.	Urocortin-2 showed augmentation of CO (UNICORN trial)	More clinical studies needed	Chan, Frampton, Crozier, Troughton, and Richards (2013)

BP = blood pressure; CD-NP = synthetic chimeric peptide; CKD = chronic kidney disease; CO = cardiac output; ESC = European Society of Cardiology; GFR = glomerular filtration rate; HF = heart failure; LV = left ventricle; LVAD = left ventricular assist device; MRAs = mineralocorticoid receptor antagonists; NO = nitric oxide; NP = natriuretic peptides; PCWP = pulmonary capillary wedge pressure; SERCA2a = sarcoplasmic reticulum Ca^{++} ATPase-2a; SGLT2 = sodium glucose cotransporter 2; UOP = urine output; VEGF = vascular endothelial growth factor.

[a] Recommendations are presented as class (level of evidence); refer to ACCF/AHA and ESC guidelines classes (Ponikowski et al., 2016; Yancy et al., 2013).

In October 2013, the RELAX-AHF-2 trial was launched with a plan to enroll 6800 patients to assess the 180-day mortality and worsening HF at 5 days. The study is currently underway, hoping to come up with answers that will determine the future of serelaxin in AHF.

5.2. Omecamtive mecarbil

Omecamtive mecarbil (OM) selectively accelerates the conversion of the actin-myosin complex from a weakly bound, to a strongly bound state (Fig. 3). It reduces the non-productive ATP hydrolysis, increases duration of systole with increased stroke volume, and improves myocardial systolic function without an increase in the oxygen consumption. OM is different from other conventional inotropes as its action is not dependent on increasing the intracellular calcium, and because it leads to an increase not only in the strength, but also in the duration of contraction, an effect that raises a concern about a possible reduction in the coronary perfusion due to the shorter diastolic time (Aronson & Krum, 2012). Early phase I clinical trials showed a dose-dependent improvement of myocardial function in healthy individuals that received OM infusion (Table 3) (Teerlink et al., 2011). OM also showed a concentration-dependent effect on myocardial performance in a phase II double-blind, placebo-controlled clinical trial that included 45 stable HF patients with EF ≤ 40% that were given the medication for 2, 24 or 72 h (Cleland et al., 2011).

COSMIC-HF is a phase II, placebo controlled clinical trial that included 448 chronic stable HFrEF patients and showed similar improvement in myocardial function. The study medication was associated with higher troponin I levels, but with no clinical myocardial ischemia or infarction reported (Teerlink et al., 2016). Another phase II clinical trial (ATOMIC-AHF) enrolled 613 HFrEF patients hospitalized for acute heart failure and randomized to receive OM for 48 h in 3 escalating doses. There was an improvement in the dyspnea reported only in the higher concentration group (OM concentration of 310 ng/mL) (Valentova & von Haehling, 2014). The launching of the phase III clinical outcomes trial was announced in September 2016.

5.3. Empagliflozin

Empagliflozin is an anti-diabetic medication that selectively inhibits the sodium glucose cotransporter 2 (SGLT2) and leads to an increased urinary glucose excretion (Heise et al., 2013). It also acts as an osmotic diuretic that reduces body weight and blood pressure (Kovacs et al., 2014; Tikkanen et al., 2015). The EMPA-REG OUTCOME trial included over 7000 patients with diabetes type 2 and high CV risk that were randomized to receive empagliflozin in addition to standard of care (Table 3). The study showed a significant improvement in the composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, hospitalization for heart failure, and of death from any cause in the treatment group (Zinman et al., 2015). A post hoc analysis of the EMPA-REG OUTCOME trial looked at a subgroup of 706 patients with heart failure at baseline and showed a significantly lower rate of cardiovascular death, HF hospitalization and all cause hospitalization in patients treated with empagliflozin compared to placebo (Fitchett et al., 2016). A clinical outcome trial is currently underway investigating the use of empagliflozin in chronic HF patients with or without diabetes.

5.4. SERCA2a activator

Because of the central role that calcium plays as a regulator of the excitation-contraction coupling, which drives the cardiac muscle contraction, the changes in the cytosolic calcium concentration can have a

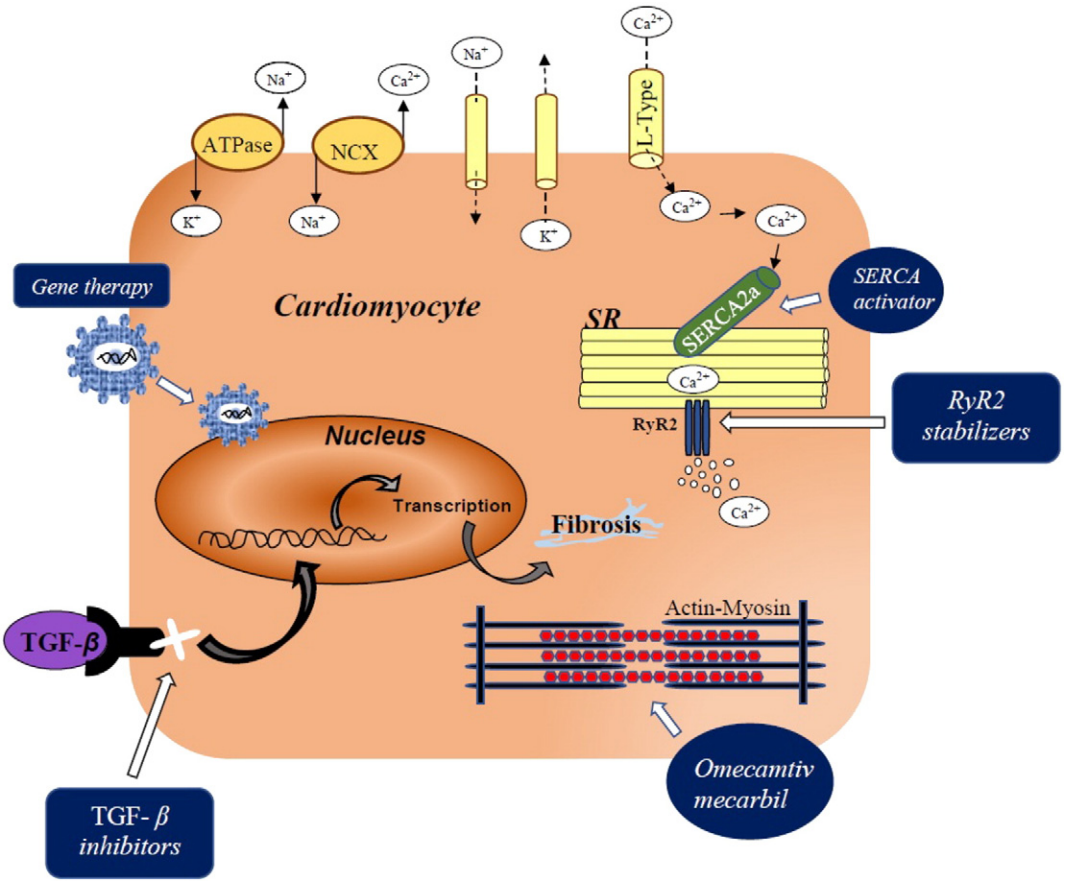

Fig. 3. Novel agents in HF — mechanism of action of some of the novel agents in clinical trials and future potential treatment targets. NCX = Na^{+}-Ca^{++} exchanger; RyR = ryanodine receptor; SR = sarcoplasmic reticulum; SERCA = sarcoplasmic reticulum Ca^{++} ATPase-2; TGF-β = transforming growth factor-β.

significant effect on the myocardial contraction. Ryanodine channels are responsible for the release of calcium in the myocardial cell (Fig. 3), while calcium reuptake is done by the sarcoplasmic reticulum through a specialized calcium pump (SERCA2a) (Periasamy et al., 2008). In HF there are many changes to the intracellular calcium, including depletion of calcium from the SR, abnormal behavior of the calcium channels, increased diastolic calcium leak, upregulation of the sarcolemmal NCX, and downregulation of SERCA (Bers et al., 2003).

Heart failure patients with over expression of their SERCA2a in cardiac myocytes was shown to have an improved contraction velocity and decreased diastolic calcium leak, which suggested that SERCA2a could be a potential therapy for HF. The CUPID study (Calcium Upregulation of Percutaneous administration of gene treatment in cardiac Disease) study was a double blind placebo controlled trial that evaluated the effectiveness of gene transfer vector using adeno-associated virus (AAV1) for delivery of SERCA2 complimentary DNA (Jessup et al., 2011). Patients who have antibodies to the naturally occurring adeno virus were excluded from the study. The groups met the prescribed criteria for efficacy, although it was noted that a larger number of patients will be required to determine the safety of SERCA2a gene therapy and its hazards, including arrythmia, which is a potential risk associated with the overexpression of SERCA2a.

CUPID2 is a randomized, double blind, placebo-controlled trial that evaluated the effect of a single intracoronary infusion of AAV1/SERCA2a on HF patients compared to placebo. The trial failed to achieve its primary endpoint of reducing HF-related hospitalizations or ambulatory treatment for worsening heart failure. Istaroxime is another SERCA2a activator that showed a significant reduction in PCWP in a phase II randomized clinical trial that included 120 patients admitted to the hospital for decompensated HFrEF (Shah et al., 2009; Sikkel, Hayward, Macleod, Harding, & Lyon, 2014). The SERCA-LVAD trial is currently underway evaluating the effect of SERCA2a on chronic HF patients on LVAD, regardless of their baseline viral antibody status (Davenport, 2016).

5.5. Novel aldosterone blockers

5.5.1. Mineralocorticoid antagonists

Mineralocorticoid receptors in the endothelial cells and myeloid cells regulate the process of cardiac hypertrophy and fibrosis (Rickard et al., 2014; Usher, Duan, & Ivaschenko, 2010). A number of non-steroidal, more selective mineralocorticoid receptor antagonists have been developed and showed some advantages over conventional MRAs in preclinical trials. These advantages included a greater reduction in blood pressure, more renal protection, and less impact on serum potassium levels (Peter, Christina, & Frank, 2015). Finerenone is a novel MRA that was investigated for use in chronic HF patients with CKD in a phase-II clinical trial and shown to be at least as effective as spironolactone in decreasing natriuretic peptide levels, with significantly lower incidence of hyperkalemia and worsening renal functions (Pitt et al., 2013). Larger size RCTs will be needed to demonstrate the safety and efficacy of novel MRAs in treating HF.

5.5.2. Aldosterone synthase inhibitor

An alternative to MR antagonism is to block aldosterone synthase. Aldosterone synthase is responsible for the enzymatic conversion of deoxycorticosterone to aldosterone (Lenzini, Seccia, & Aldighieri, 2007). In heart failure, aldosterone synthase regulates the local production of aldosterone in the heart muscle in proportion to the severity of HF (He & Anderson, 2013). Preclinical data showed that the aldosterone synthase inhibitor improved cardiac hemodynamic parameters as well as LV function, and prevented progressive LV remodeling in a rat

model of HF (Mulder et al., 2008). Clinical data will be needed to show the benefits of aldosterone synthase inhibitors in this patient population.

5.6. CD-NP

CD-NP is synthetic natriuretic peptide that causes diuresis, natriuresis, and vasodilation with a minimal effect on blood pressure (Fig. 1). In addition, CD-NP was reported to have an inhibitory effect on the cardiac fibroblastic proliferation (Lisy, Huntley, McCormick, Kurlansky, & Burnett, 2008). A phase I clinical trial in 22 normal subjects showed that CD-NP causes aldosterone suppression with an increase in renal sodium excretion, and a minimal reduction in BP (Lee et al., 2009). The anti-fibrotic effect of CD-NP was also demonstrated in humans with end-stage HF patients, with and without LVAD (Ichiki et al., 2014). Interim data from phase IIa clinical trial in patients with AHF showed a significant reduction in PCWP with a significant increase in urine output. There was no significant drop in blood pressure or worsening renal functions with the use of CD-NP (press release of Nile Therapeutics, 10/2008).

5.7. Urocortin

Corticotropin-releasing factor (CRF) is a peptide that is released by the body in response to stress, and causes a multitude of systemic effects that include vasodilation, anti-inflammatory effect, as well as chronotropic and inotropic effects (Stengel & Taché, 2010). Urocortin-2 is one of the CRF family members that has a high affinity to CRF receptors (Vaughan et al., 1995). Urocortin was shown to improve myocardial function and increase the ventricular fibrillation threshold in an animal model with severe systolic heart failure (Silvia et al., 2010). A randomized, single center, double-blind clinical trial (UNICORN) that included 53 acute HF patients showed a significant augmentation of cardiac output in those receiving urocortin-2 compared to placebo (Chan et al., 2013). There was a significant drop in systolic blood pressure in the treatment group, with no remarkable decrease in pulmonary artery pressure and pulmonary capillary wedge pressure. A larger size, multicenter RCT will be needed to further investigate the safety and efficacy of urocortin use in HF.

6. Agents with questionable risk/benefit profile

6.1. Synthetic natriuretic peptides

Nesiritide is a synthetic form of the human BNP. The effect of nesiritide in patients with AHF was investigated in the VMAC trial (Publication Committee for the VMAC, 2002), which included 498 patients that were randomized to receive nesiritide vs. nitroglycerine (NTG) vs. placebo. Nesiritide showed a significant decrease in PCWP and PAP compared to NTG and placebo, and a significant improvement in dyspnea compared to placebo but not to NTG. The use of nesiritide became very popular following the VMAC study results, although that was changed after a couple of reports that came out to show an increase in 30-day mortality and worsening of renal functions associated with the use of nesiritide in AHF (Sackner-Bernstein, Kowalski, Fox, & Aaronson, 2005; Sackner-Bernstein, Skopicki, & Aaronson, 2005). The ASCEND-HF trial included over 7000 patients and investigated the safety and efficacy of using nesiritide in AHF. Although the study didn't show any worsening in mortality or renal function associated with the use of nesiritide, there was no statistically significant improvement of dyspnea (O'Connor et al., 2011).

Multiple synthetic forms of ANP, including anaritide and carperitide, were developed and tested in humans but failed to show any significant changes in urine output and sodium excretion in patients with HF (Potter, Yoder, Flora, Antos, & Dickey, 2009).

6.2. Ularitide

Urodilatin is a pro atrial natriuretic peptide that is produced by the distal renal tubules (Fig. 2) (Forssmann, Richter, & Meyer, 1998). Ularitide is a synthetic form of urodilatin that stimulates renal excretion of sodium and water, causes systemic vasodilation, and is more resistant to degradation (Mitrovic et al., 2013; Vesely, 2007). In an animal model of HF, ularitide showed an increase in the glomerular filtration rate (GFR), urinary flow, and sodium excretion. The use of ularitide was also associated with a significant drop in pulmonary artery pressure, right atrial pressure, and pulmonary capillary wedge pressure (Anker, Ponikowski, Mitrovic, Peacock, & Filippatos, 2015). Ularitide showed an improvement in dyspnea and a decrease in PCWP in a phase IIb RCT that included 221 AHF patients (Mitrovic, Seferovic, & Simeunovic, 2006).

In a phase III double blind placebo controlled clinical trial (TRUE-AHF) that enrolled 2157 AHF patients, the use of ularitide was associated with less worsening of HF at 48 h and a 47% decline in pro-BNP compared to placebo. There was a significant improvement in the marker of vascular congestion (including hemoglobin, serum creatinine and hepatic transaminases), although there was no difference in cardiovascular mortality at a median follow up of 15 months, and no significant difference in all-cause mortality at 30-day follow up (TRUE-AHF, 2016). Patients receiving ularitide had more hypotension compared to the placebo group. These findings are consistent with the previously reported outcomes of other forms of synthetic natriuretic peptide, i.e. nesiritide.

6.3. Adenosine receptor antagonists

There are four subtypes of adenosine receptors (A_1, A_{2A}, A_{2B}, and A_3), and these receptors are found in multiple body organs and contribute to a wide range of physiological and pathological processes including cardiac rhythm, vascular tone, coronary blood flow, renal blood flow, and many more (Fredholm, 2011). Adenosine has been in clinical use for a long time, both as an agent to treat and facilitate the diagnosis of supraventricular arrhythmias, and as a vasodilator in myocardial perfusion imaging studies (Delacretaz, 2006; Ghimire, Hage, Heo, & Iskandrian, 2013). The suggested use of adenosine antagonists in HF was based on multiple observations, including the elevation of adenosine levels in patients with HF, the data from animal studies that supported a potential role for adenosine antagonism in improving renal functions in patients with acute HF, and the tolerability and safety profile of caffeine; a widely used adenosine antagonist (Funaya et al., 1997; Jacobson, von Lubitz, Daly, & Fredholm, 1996; Ribeiro & Sebastião, 2010; Sun, 2001). Unfortunately, multiple clinical trials failed to provide a supportive evidence on the benefits of adenosine antagonists in AHF to improve renal functions, with some concerns raised about the increased incidence of stroke and seizures with the use of adenosine A_1 receptor antagonists (Teerlink, 2012, Voors, 2011).

The failure of adenosine antagonists to show a favorable effect in humans was due to multiple factors including the complexity of the adenosine signaling pathway, the development of tolerance to adenosine receptor legends, and the state of adenosine antagonism that many HF patients have due to the widespread use of caffeine worldwide (Chen, Eltzschig, & Fredholm, 2013). Novel ways to perform adenosine antagonism, including an organ-specific approach and a multi-target approach, might represent new hopes in using this group of medications to treat patients with HFrEF.

6.4. Statins

Statins are hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that were shown to reduce cardiovascular events in patients with dyslipidemia with or without coronary artery disease (Lim, 2013). Statins also have a pleiotropic effect that causes a decrease in

the inflammatory markers (Wallace, Stetson, & Kucuker, 2005; Zhang et al., 2010), which might play a major role in their ability to improve cardiovascular outcomes. Unfortunately, the role of statins in HF patients with no coronary artery disease has not been identified yet due to the conflicting evidence. The early data on the benefits of using statins in heart failure came from relatively small clinical trials (Domanski, Coady, & Fleg, 2007; Horwich, MacLellan, & Fonarow, 2004), which were followed by two large-sized clinical trials, CORONA and GISSI-HF trials, both of which failed to show any improvement in the outcomes of HF with statins (Kjekshus, Apetrei, & Barrios, 2007; Tavazzi, Maggioni, & Marchioli, 2008). A subgroup analysis of the CORONA trial showed that HFrEF patients with elevated inflammatory markers (high sensitivity CRP) at baseline might benefit from using rosuvastatin (McMurray, Kjekshus, & Gullestad, 2009), which is consistent with some earlier reports on the importance of the anti-inflammatory effect of statins in improving cardiovascular outcomes. At this point, we need a large sized, well-designed RCT to provide answers regarding the potential benefits of statins in selective HFrEF patients.

6.5. Phosphodiesterase-5 inhibitors

By inhibiting the degradation of cyclic GMP, Phosphodiesterase-5 (PDE5) inhibitors cause an increase in the intracellular cGMP levels that results in pulmonary and systemic vasodilation. PDE5 inhibitors are approved for use in patients with erectile dysfunction and pulmonary hypertension (Schwartz, Jackson, Stecher, Campoli-Richards, & Kloner, 2013). Multiple small size studies showed that PDE5 inhibitors can improve symptoms of HF, quality of life, cardiac index, 6-minute walk test, and decreased systemic vascular resistance (Schwartz, Levine, & Comstock, 2012). PDE5 inhibitors also showed an improvement in exercise capacity in HFrEF patients with secondary pulmonary hypertension (Lewis, Shah, & Shahzad, 2007). A recent meta-analysis consisted of 612 patients from 9 RCTs showing an improvement in peak VO2, VO2 at anaerobic threshold and ejection fraction in patients with HFrEF taking PDE5 inhibitors (Zhuang et al., 2014). A larger size RCT will be needed to confirm the utility of PDE5 inhibitors in improving symptoms of HF, and to investigate any potential impact on the outcomes.

6.6. Endothelin receptor antagonists

Endothelin-1 (ET-1) receptor antagonists are used in the treatment of patients with pulmonary arterial hypertension (PAH, WHO Group 1) to improve symptoms (Galié, Manes, & Branzi, 2004). ET-1 receptor antagonists induce pulmonary and systemic vasodilation by selectively (i.e. ambrisentan) or non-selectively (i.e. bosentan and macitentan) blocking ET-1 receptors in order to antagonize the vasoconstrictive effect of circulating ET-1, which was shown to be elevated in patients with PAH (Davenport et al., 2016; Stewart, Levy, Cernacek, & Langleben, 1991).

Multiple ET-1 receptor antagonists were tested in patients with HFrEF and failed to achieve their goals, for example, the EARTH trial was a double blind, placebo-controlled trial that randomized 642 patients to received darusentan vs. placebo. The study didn't show any difference in cardiac remodeling, symptoms or clinical outcomes between the treatment groups (Anand et al., 2004). The use of bosentan in pulmonary hypertension secondary to HFrEF was evaluated in a randomized, double-blind, placebo-controlled study that included 94 patients with EF < 35%, and failed to show any measurable hemodynamic benefits (Kaluski et al., 2008). Another open label study that included 17 patients who were given bosentan showed a reduction in pulmonary artery pressure and pulmonary vascular resistance with no significant changes in cardiac output or cardiac index, with one third of the patients (6 patients) discontinuing the therapy because of the side effects, which included ADHF, hypotension and elevated liver enzymes (Padeletti et al., 2013).

7. Future potential treatment targets

7.1. Anti-inflammatory medications and medications affecting cytokine pathways

Although the contribution of the immune system to the development and disease progression of HF is not very well understood, there is plenty of evidence on an inflammatory component to the syndrome of HF that predicts clinical outcomes (Dick & Epelman, 2016). Multiple immunomodulatory approaches to treating HF, including intravenous immunoglobulin (IVIG), pentoxifylline, therapeutic plasma exchange, and other non-specific immune-modulation therapies have been tested in small-sized clinical trials. Data obtained from these trials showed some promising outcomes in terms of an improvement in ejection fraction, symptomatic improvement, and even a decrease in hospitalization and mortality, although the evidence is not sufficient to draw conclusions on the benefits and safety of the long-term immunomodulation in HF (Flores-Arredondo, García-Rivas, & Torre-Amione, 2011). Celecade is a unique approach, where patient's own blood cells were stressed to induce cell death and then reinjected in the patient. This approach was shown to have mortality benefits in a subgroup of patients with non-ischemic cardiomyopathy and NYHA-II symptoms, although a larger size RCT is needed to confirm the results (Torre-Amione, Anker, & Bourge, 2008).

7.2. Anti-fibrotic agents

Fibrosis plays an essential role in the ventricular remodeling and the progress of HF (Swynghedauw, 1999). Transforming growth factor-β (TGF-β) is a profibrotic cytokine that was shown to play a major role in the development of cardiac fibrosis and hypertrophy (Bujak & Frangogiannis, 2007). It was also shown that the expression levels of TGF-β1 mRNA were increased in hypertrophic cardiomyopathy and dilated cardiomyopathy (Li et al., 1997; Pauschinger et al., 1999). The inhibition of TGF-β in a rat model after MI was shown to prevent fibrosis and improve myocardial function (Fig. 3) (Kuwahara et al., 2002; Okada et al., 2005). There are multiple TGF-β inhibitors that were developed and used in clinical trials to treat other fibrotic conditions. For example pirfenidone, a TGF-β inhibitor that was shown to attenuate left atrial remodeling in a canine model, was used to treat patients with idiopathic pulmonary fibrosis but failed to show improvement in outcomes and was associated with a very high rate of GI symptoms (nausea, vomiting, and dyspepsia) (Azuma et al., 2005; Lee et al., 2006). Other new anti-fibrotic agents have been developed and tested in animal models with good results, but clinical studies are needed to demonstrate their effect on outcomes in humans.

7.3. Ryanodine receptor stabilizer — JTV519

As discussed earlier, Ryanodine channels are responsible for the release of calcium inside the myocardial cell (Fig. 3). The function of the Ryanodine receptors (RyR2) is controlled by a protein called Calstabin, which gives stability to the RyR2 receptors during the resting state, while its dissociation allows RyR2 receptors to be phosphorylated and to start releasing calcium (Danila & Hamilton, 2005). A diastolic calcium leak through RyR2 has been described in patients with HF and is thought to be due to the chronic adrenergic activation that creates a state of hyperphosphorylation. This state of hyperphosphorylation leads to calstabin2-depleted channels with a pathological increase in the open probability under resting conditions, which leads to the diastolic calcium leak (Eisner & Trafford, 2002). Multiple RyR2 stabilizers were developed and showed that they can effectively enhance the RyR2-calstabin binding, and stabilize the closed state of RyR2 in animals (Hasenfuss & Seidler, 2003). Human studies are needed to demonstrate the safety and efficacy of this group of medications for use in patients with HF.

7.4. Gene therapy

Gene therapy represents a potential paradigm shift in the way HF is treated, with the hope that it will offer a cure for certain types of HF that are caused by genetic mutation, and stop disease progression or enhance myocardial disease regression in other forms of HF (Pleger et al., 2013). The heart was thought to be an optimal organ for gene therapy given its anatomical position and accessibility (Raake et al., 2011), although the road to bringing a safe and efficient form of gene therapy to clinical practice was not easy. The main challenge that faces gene therapy is the delivery vehicle that will carry the gene and introduce it to the target cell's DNA, which can either be a viral or a non-viral vehicle. Viral vectors are immunogenic and can lead to inflammation, degeneration, and mutations. On the other hand, non-viral vectors are safe and less immunogenic, but they produce a less efficient gene transduction compared to viral vectors (Nayerossadat, Maedeh, & Ali, 2012).

As discussed earlier; SERCA2a gene therapy delivered via an adeno-associated virus vector is one example that has already made its way to clinical trials, although its favorable effect on outcomes is yet to be proven. A large number of viral and non-viral vectors are currently investigated and can provide the hope for a new era of genetic therapies in HF that are both safe and effective (Tilemann, Ishikawa, Weber, & Hajjar, 2012).

8. Conclusion and perspectives

Many medical therapies were introduced since the 1980s and have led to a modest improvement in the survival and quality of life of patients with HFrEF. The mechanism of action of these agents mainly focuses on supporting the circulation in acute HF, and on counteracting the compensatory mechanisms that take place in the chronic setting (mainly the RAAS and sympathetic system activation), without any meaningful success in reversing the underlying myocardial disease process. Multiple new therapeutic agents, including RyR2 stabilizers, anti-fibrotic agents and gene therapy, represent a new hope in treating heart failure using approaches that target some of the disease processes inside the myocardium rather than targeting the body reactions to myocardial dysfunction.

Despite the significant expansion of our armamentarium of HFrEF medications, the stakes are getting even higher with a reported increase in the prevalence of heart failure and its cost on the healthcare system. As noted in his published lecture in 1997, Dr. Braunwald described HF as one of the rising epidemics of our time (Braunwald, 1997). There are two major components to the HF epidemic (Fig. 4). The first one is the increased incidence of HF, fueled by the high prevalence of cardiovascular risk factors in the community, including hypertension, obesity, diabetes mellitus, smoking, along with aging of the population and the advancements in treating myocardial infarction and other cardiac conditions. All these have led to a larger number of patients surviving with abnormal hearts (Bui, Horwich, & Fonarow, 2011; Roger, 2013). The second component is the improved survival of patients diagnosed with HF thanks to the recent advancements in device and drug therapies.

The future of research in heart failure should focus on exploring new therapeutic avenues that can improve quality of life, survival, and decrease the cost of treating patients with HF. Some examples of that would be interventions that can reverse myocardial remodeling and fibrosis, cell based and gene based therapies, circulatory support devices as an alternative to cardiac transplant, along with applying more aggressive measures for the prevention and early detection of cardiovascular diseases (Udelson & Stevenson, 2016). Personalized medicine is another growing concept in HF that involves tailoring of medical management according to the patient's genetic information (Mestroni & Taylor, 2011). This approach might have a tremendous value in treating

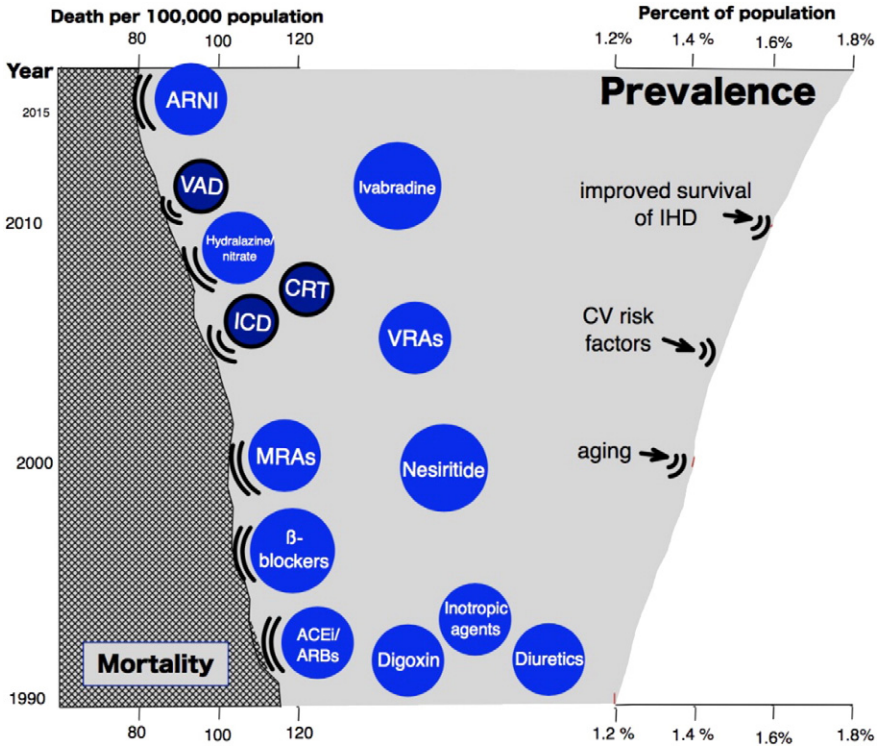

Fig. 4. HF and pharmacotherapy overtime — a visual representation of the increased prevalence of heart failure in the US over time, with a reduction of mortality (left-hand side) due to the recent advancements in drug and device therapies, and an increase in incidence of heart failure (right-hand side) that resulted from many factors including aging of the population, increased prevalence of cardiovascular risk factors, and improved survival of patients with ischemic heart disease. Medications in the center of this figure are used for symptomatic relief with no proven impact on mortality. ACEi = angiotensin converting enzyme inhibitors; ARBs = angiotensin receptor blockers; ARNI = angiotensin receptor blocker-neprilysin inhibitor; CRT = cardiac resynchronization therapy; CV = cardiovascular; ICD = implantable cardioverter defibrillator; IHD = ischemic heart disease; MRAs = mineralocorticoid receptor antagonists; NG = nitroglycerin; SNP = sodium nitroprusside; VRAs = vasopressin receptor antagonists; VAD = ventricular assist devices.

patients with hereditary forms of dilated cardiomyopathy, adjusting the HF pharmacotherapeutic regimen to the patient's genetic profile to achieve maximum benefit, and even predicting the disease progression patterns and outcomes in individual patients.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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