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Role of New Therapies in Reducing Mortality and Major Morbidity in Patients with Systolic Heart Failure

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Abstract

Though heart failure therapies, particularly for systolic heart failure, have developed rapidly and markedly during the past four decades, a need for additional relief persists and is progressively being met. Two new drugs have been approved for marketing in the United States within the past two years, and two other glucose lowering therapies for diabetes appear to have efficacy for heart failure as well. In addition, device therapy for heart failure has progressed markedly during the past 5 years, particularly in refinements of the indications and applications of devices to minimize symptoms and hospitalizations and to maximize survival. This chapter will outline these recent developments.

Keywords: cardiovascular pharmacology, cardiovascular devices, angiotensin receptor blocker neprilysin inhibitor (ARNI), heart rate slowing, glucagon-like peptide receptor agonist

1. Introduction

Heart failure affects almost 6 million Americans [1], of whom 1 million are hospitalized for heart failure annually [2]. According to latest available data published in June 2016 in the National Vital Statistics Report, in 2014 cardiovascular diseases were the leading causes of death in the United States, responsible for 803,227 deaths of which 68,626 (8.5%) were related to heart failure [3]. Recent therapeutic advances suggest the potential for important amelioration of these outcomes when the new therapies are added to conventional modalities. In this chapter we will review the recent data supporting the incorporation of these new therapies into clinical practice.

2. Ivabradine

In April 2015, FDA approved ivabradine for reduction of heart failure hospitalizations for patients with heart failure with reduced ejection fraction (HFrEF) [4].

Ivabradine selectively blocks sinoatrial nodal cell hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and, consequently, blocks the resulting transmembrane current (I_f) by entering and binding to a site in the channel pore from the intracellular side [5, 6]. In the United States, it is currently indicated for reduction in heart failure hospitalizations in patients with symptomatic chronic heart failure with ejection fraction $\leq 35\%$ who are in sinus rhythm, with heart rate ≥ 70 beats per minute who already are being treated with maximally tolerated β -blockade [7] (as well as other conventional drugs for HFrEF). The drug now is recommended in the updated AHA-ACC guidelines for treatment of patients with HFrEF (class IIa recommendation, level of evidence B-R) [8]. In several other countries, the drug also is indicated for reduction in mortality or heart failure hospitalizations in patients with HFrEF, and also to prevent angina pectoris in symptomatic patients with chronic stable coronary artery disease irrespective of heart failure.

Ivabradine is unique in that it targets the HCN channel subtype found predominantly in sinoatrial nodal cells [9] and, thus, has little effect elsewhere in the heart or in other tissues (though drug action on HCN channels in the retina, similar to those in the sinoatrial node, is believed to underlie the side effect of visual phosphenes [flashing scotomata] reported in 3% of patients in the Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial [SHIFT]). This locus of activity differs from that of β -blockers, which also slow heart rate but act wherever β -receptors are present (e.g., in the ventricles, causing negative inotropy, in the bronchi, causing bronchoconstriction, etc.) and from calcium channel blockers, the action of which, in the heart and smooth muscle, can cause negative inotropy, hypotension, and constipation. Ivabradine is a selective and specific inhibitor of the myocardial I_f , a current involved in modulating the cardiac pacemaker current [10]. At therapeutic concentrations, both in animals and humans, ivabradine does not affect any other cardiac channel or current (including those involving Na^+ , K^+ , or Ca^{2+}) [6].

To be active, ivabradine needs to penetrate the HCN channels; this requires appropriate orientation of the channel components, which occurs when the channel is hyperpolarized to $[-40 \text{ mV}]$. Thus, the relevant channels are hyperpolarization-activated. As heart rate increases, the time during which the channels are hyperpolarized, and thus open to ivabradine, increases. Consequently, ivabradine-mediated heart rate reduction is “use dependent,” i.e., it is more pronounced as heart rate increases [9].

Dosage: The evidence-based and recommended maximal dose of ivabradine is 7.5 mg twice daily [11]; the recommended starting dose of 5 mg twice daily.

Clinical evidence: Evidence supporting the utility of ivabradine for HFrEF primarily derives from SHIFT. The study was an event-driven, multinational, randomized, double-blinded, parallel-group trial in patients in sinus rhythm with heart rate ≥ 70 beats/min with moderate-to-severe heart failure and left ventricular ejection fraction $\leq 35\%$ [11].

The study involved 6505 patients (53 of the original 6558 patients were censored for a major protocol violation) from 677 centers in 37 countries. Participants were randomized to ivabradine titrated to a maximum of 7.5 mg twice daily or to matched placebo and were followed for a median of 22.9 months and a maximum of 42 months [11, 13].

Study subjects were at least 18 years old (male and female) with symptomatically stable heart failure (and drug therapy) for at least 4 weeks and a hospitalization for worsening heart failure within the previous 12 months [11].

Treatment with ivabradine was associated with a placebo-subtracted average reduction in heart rate of 10.9 bpm at 1 month after randomization and 9.1 bpm at 1 year. The SHIFT primary composite endpoint (cardiovascular death or first hospitalization for worsening heart failure) was reduced by 18% (hazard ratio, 0.82 [95% CI, 0.75–0.90], $p < 0.0001$), driven primarily by reduction in hospitalizations for worsening heart failure (26% reduction, hazard ratio, 0.74 [95% CI, 0.66–0.83], $p < 0.0001$). Death from heart failure fell to 26% (hazard ratio, 0.74 [95% CI, 0.58–0.94], $p = 0.014$).

From 1 year onward, at least 70% of patients were at the target dose of ivabradine (7.5 mg twice daily). By contrast, only 49% of the 6505 patients enrolled in the trial were able to reach at least 50% of evidence-based target β -blocker dose at baseline (90% were receiving at least some dose of beta blocker) because of contraindications or poor tolerability [11].

Cardiovascular and all-cause deaths were not significantly reduced by ivabradine [11], though, numerically, a 9% reduction in cardiovascular death was observed in the ivabradine group. (However, in Europe, the European Medicines Agency ordered a reanalysis of the data with entry at heart rate ≥ 75 bpm. This analysis revealed significant reduction in mortality as well as in hospitalizations. As a result, approval in Europe is for patients with symptomatic heart failure and LVEF $\leq 35\%$ in sinus rhythm with heart rate ≥ 75 bpm.)

Sudden cardiac death was not affected by ivabradine, perhaps because of the effect of the background β -blocker treatment, which, unlike ivabradine, has intrinsic electrophysiological effects and is known to affect sudden cardiac death [11].

Postulated mechanisms of benefit from ivabradine-mediated heart rate reduction include decreased myocyte ischemia, improving the balance between myocardial oxygen (and energy) supply and demand; this effect is attributable not only to reduction in demand but also to increased supply caused by lengthening duration of diastole during which coronary flow occurs, and lack of negative lusitropy (relaxation, an active process that is inhibited by ischemia and also by beta blockade) reducing impedance to coronary flow relative to beta blockade [12]; other data suggest that use of the drug also increases endothelial cell proliferation, endothelial nitric oxide synthase (eNOS) activity, and increased collateral function [13].

The most prominent adverse effects of ivabradine are excessive bradycardia [14–16], atrial fibrillation [14, 15], and phosphenes (visual brightness in one portion of the visual field) [15, 16], and a small but significant increase in systolic blood pressure (the clinical importance of which is not clear) [15]. In SHIFT, the drug was not studied in patients with acute decompensated heart failure and thus is not indicated for such patients, through recent data [17, 18]

suggest that beginning the drug early during a hospitalization for acute decompensated heart failure is acceptably safe and is effective in lowering heart rate. The drug also is contraindicated in patients with blood pressure less than 90/50 mmHg, and in the presence of sick sinus syndrome, sinoatrial block, or third degree AV block, unless a functioning demand pacemaker is present, and in patients with severe hepatic impairment or concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors or enhancers (ivabradine is metabolized in the liver by the P450 CYP 3A4 system). Because the target heart rate (supported by the SHIFT data [11]) is 50–60 bpm, the drug should not be given if the pretherapy heart rate already is ≤ 60 bpm; also, ivabradine is contraindicated (because it would have no effect) in patients who are pacemaker dependent (heart rate maintained exclusively by the pacemaker). Animal studies indicate the potential for fetal cardiac malformations if given during pregnancy [15]; therefore, its use is contraindicated during pregnancy and, if used in nonpregnant women of child-bearing age, effective contraception should be assured. At doses up to 10 mg BID, ivabradine prolongs the uncorrected QT interval; however, when appropriately corrected for heart rate, this increase does not exceed 2 ms, precluding direct proarrhythmic potential [16].

3. Sacubitril-valsartan

In July 2015, a few months after approval of ivabradine, FDA approved sacubitril-valsartan, also for treatment of patients with HFrEF [19].

Sacubitril-valsartan is a combination of an already approved angiotensin receptor blocker (valsartan) and a neprilysin inhibitor (such combination drugs are now known as ARNIs).

Neprilysin is a neutral endopeptidase and plays an important role in pathogenesis of heart failure and hypertension by catalyzing the degradation of endogenous vasoactive peptides, such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), endothelin-1 (ET-1), angiotensin II, and bradykinin [20]. Inhibition of neprilysin raises blood concentrations of these vasoactive peptides, some of which have potentially beneficial hemodynamic effects in patients with heart failure [20].

Inhibition of this neutral endopeptidase promotes sodium and water excretion by inhibiting sodium reabsorption in the proximal and distal nephron [21], and can cause reduction in systemic vascular resistance, pulmonary artery pressure, and pulmonary capillary wedge pressure. Blockage of neprilysin is associated with arterial stiffness reduction, enhanced endothelial function, and cardiac antihypertrophic and antifibrotic effects [13, 21]. Sacubitril-valsartan also has inhibitory actions on the renin-angiotensin-aldosterone system and sympathetic nervous system [13, 21].

FDA has approved marketing of the new ARNI for reduction in mortality and heart failure hospitalizations in patients with chronic heart failure (NYHA Class II–IV) and at least moderately subnormal ejection fraction ($<40\%$) and the AHA-ACC Updated Heart Failure Guideline recommend its use for this indication [8, 22]. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI

is guideline-recommended to further reduce morbidity and mortality (strength of recommendation I and level of evidence B-R) [8].

Dosage: The initial dose of 24/26 mg twice daily is recommended for patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents. The dose can be doubled every 2–4 weeks, as tolerated, to reach the target maintenance dose of 97/103 mg twice daily [22].

Clinical evidence: The evidence supporting the efficacy of this ARNI was shown in the Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial [23].

The study included 8442 randomized patients with chronic heart failure (NYHA Class II–IV) and ejection fraction $\leq 40\%$. Patients received either a combination of valsartan and sacubitril (200 mg [97/103 mg] twice daily) or the ACE inhibitor enalapril (10 mg twice daily) in addition to other guidelines-recommended therapy. The trial was stopped early due to highly significant benefit of sacubitril-valsartan without excessive adversity.

The composite endpoint (cardiovascular death and heart failure hospitalizations) was reduced by 20%, as were both components of this endpoint (CV death reduction: hazard ratio, 0.80 [95% CI, 0.71–0.89] $p < 0.001$, heart failure hospitalizations reduction: hazard ratio, 0.79 [95% CI, 0.71–0.89] $p < 0.001$). Death from any cause also was reduced by sacubitril-valsartan by 16% ($p < 0.001$).

During PARADIGM-HF most adverse events were more frequent on the already approved enalapril than on the ARNI combination drug. Of those of greatest concern (hypotension, renal insufficiency, angioedema, and hyperkalemia) only hypotension was significantly more frequent with sacubitril-valsartan, while angioedema, though more frequent with the combination (and known to be a potential consequence of neprilysin inhibition), occurred relatively infrequently [8, 22]. As a result of these findings, the combination is contraindicated in patients with a history of angioedema. It is also contraindicated during pregnancy, and if an ACE inhibitor has been administered within 36 hours of switching to the ARNI or if patients currently are receiving ACE inhibitors or have diabetes and are taking aliskerin [22].

4. New antidiabetic medications (liraglutide and empagliflozin)

Recent studies have shown beneficial effects of prototypes of two new groups of antidiabetic medications on cardiovascular events. Though results specifically for heart failure hospitalizations were significantly improved only with empagliflozin and did not reach statistical significance for liraglutide (studies of which had insufficient power to test the hypothesis that such events are prevented), there was clear numerical HF event reduction in patients with HFrEF with both drugs and, thus, inclusion in this chapter is appropriate.

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that enhances insulin secretion. One trial randomized 9340 patients with type 2 diabetes ($HbA_{1c} \geq 7.0\%$) and

underlying cardiovascular disease (CAD, cerebrovascular disease, PVD, CKD of stage 3 or greater, or chronic heart failure NYHA class II-III) to liraglutide or placebo on appropriate conventional background therapy [24]. The median time of exposure to liraglutide or placebo was 3.5 years. Death from cardiovascular causes (hazard ratio, 0.78 [95% CI, 0.66–0.93], $p = 0.007$), hospitalization for heart failure (hazard ratio, 0.87 [95% CI, 0.73–1.05], $p = 0.14$), and nonfatal myocardial infarction, nonfatal stroke, and death from any cause all were at least numerically lower in patients receiving liraglutide than placebo.

However, another far smaller double-blind, placebo-controlled randomized trial including 300 patients with type 2 diabetes and established HFrEF who were recently hospitalized did not reveal any beneficial effect of liraglutide [25]. The power of this trial was relatively low to find a significant difference if it existed, precluding firm conclusions about the role of liraglutide for HFrEF.

Another antidiabetic medication which may provide favorable effects on mortality and morbidity in patients with heart failure is empagliflozin, an inhibitor of the sodium glucose cotransporter-2 (SGLT-2), which enhances renal glucose excretion [26]. The placebo-controlled EMPA-REG trial assessed the effects of empagliflozin on cardiovascular morbidity and mortality in 7020 randomized patients with type 2 diabetes and established cardiovascular disease during a median follow-up of 3.1 years. Relative risk of cardiovascular death was reduced by 38% (3.7% with empagliflozin vs. 5.9% with placebo, hazard ratio, 0.62 [95% CI, 0.49–0.77], $p < 0.001$). Also, relative risk of hospitalization for heart failure was reduced by 35% (hazard ratio, 0.65 [95% CI, 0.50–0.85], $p = 0.002$). Death from any cause also was lower with empagliflozin (hazard ratio, 0.68 [95% CI, 0.57–0.82], $p < 0.001$).

5. Recent advances in device therapy

5.1. Left ventricular assist devices

Left ventricular assist devices (LVAD) are indwelling electromechanical pumps used to support cardiac function in patients with advanced heart failure. First successfully implanted in 1966 [27], such “first-generation” devices were limited by size and durability, were highly thrombogenic, and frequently complicated by infection. The mechanical design generally featured pulsatile displacement, analogous to the mechanism of pumping by the native heart [28]. More recent models have featured continuous flow with small rotating “impellers” moving blood forward. As a result, newer pumps are smaller and have no bearings (resulting in less mechanical wear and tear and greater durability than older models). Though generally introduced by thoracotomy and requiring a transcutaneous connection to an external generator, newer iterations are sufficiently slim such that they can be introduced percutaneously (the Impella device) via the femoral or axillary artery in the cardiac catheterization lab [29, 30]. Such percutaneously introduced devices have less pumping capacity than the more conventional models.

The effectiveness of LVAD was assessed in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial in 2001. The study

involved 140 patients with advanced heart failure and contraindications to heart transplantation surgery. The trial revealed a LVAD associated 48% reduction in all-cause death (the primary endpoint) compared with medical therapy (relative risk, 0.52 [95% CI, 0.34–0.78], $p = 0.001$) [31].

In subsequent trials LVAD has reduced mortality and improved quality of life and functional capacity in patients with advanced heart failure. LVADs enhance total cardiac output by adding to that of the damaged native heart, potentially allowing myocardial recovery, particularly in patients with cardiogenic shock [30–34].

LVAD implantation currently is approved by FDA as a bridge to cardiac transplantation and also as “destination therapy” in selected patients for whom transplantation may not be feasible or possible [35].

Adverse events associated with LVAD use include thrombosis and thromboembolization (potentially leading to stroke), bleeding, and infection [31, 35].

5.2. Extracorporeal membrane oxygenators (ECMO)

ECMO devices enable extracorporeal circulation and physiologic gas exchange during acute respiratory and/or cardiorespiratory failure.

Two types of ECMO have been developed: veno-arterial extracorporeal membrane oxygenators (VA-ECMO) and veno-venous extracorporeal membrane oxygenators (VV-ECMO). FDA has approved application of VA-ECMO for short-term support in patients with refractory cardiogenic shock who have an underlying potentially reversible condition, acute onset refractory cardiogenic shock unresponsive to inotropes and/or intra-aortic balloon pump counterpulsation (IABP), and extracorporeal cardiopulmonary resuscitation (ECPR) [36].

Supporting data are case series from multiple countries [36–41]. In one study involving 45 patients with refractory cardiogenic shock, ECMO was associated with survival to hospital discharge in 29% (13/45) versus the expected total absence of survival without ECMO [40]. In another series, survival was achieved in 71% of patients with refractory cardiogenic failure during severe septic shock [41].

ECMO-associated adverse events include bleeding, infection, renal failure, liver failure, need for blood transfusion, hematuria, pulmonary complications, and need for thoracotomy [36].

5.3. Cardiac resynchronization therapy (CRT)

More than 20 years of research has established the role of CRT in patients with systolic heart failure and widened QRS complex. By the 1990s, a link emerged between electrical dyssynchrony and LV function, in which conduction disturbances result in an abnormally circuitous and lengthy conduction pathway, wasted work, and a reduction in cardiac output [42].

Intraventricular systolic dyssynchrony refers to lack of normal coordination in the timing of contraction between ventricular segments [43]. Dyssynchrony can be identified by multiple imaging techniques [44]. The prevalence of dyssynchrony is directly related to QRS duration

and ventricular size and inversely related to left ventricular ejection fraction (LVEF) [43]. Prevalence of echocardiographically detectable dyssynchrony ranges from 27% in patients with QRS duration <120 ms, to 89% in those with QRS duration >150 ms [45].

CRT is effected by placing a pacemaker lead in each ventricle and setting the pacemaker generator to coordinate the stimuli to both ventricles, hence normalizing the contraction pattern. Mortality and morbidity (as well as symptoms) are consistently reduced (and LVEF and reverse remodeling improved) by CRT in patients with refractory HFrEF and prolonged QRS interval who are on optimal medical therapy [46–55].

CRT has been most clearly effective when QRS duration is abnormal, generally ≥ 150 ms with a left bundle branch block pattern, and when LVEF is $\leq 35\%$. However, recently, benefit for a wider range of patients has been explored. In BLOCK-HF, patients with HF symptoms, LVEF <50% and high degree AV block, who would otherwise be treated with RV pacing, were randomized to biventricular pacing versus RV pacing (patients who met the by then conventional more stringent CRT indications were excluded). CRT provided 26% reduction in the primary composite endpoint of total mortality, urgent HF care, or progression of increase in the LV end-systolic volume index [56].

In the randomized, double-blind LESSER-EARTH trial CRT was evaluated in patients with LVEF $\leq 35\%$ and QRS <120 ms who failed to improve in clinical outcomes or LV reverse remodeling on conventional therapy. Importantly, dyssynchrony, determined by an imaging study, was not required for inclusion in the study. The trial was terminated prematurely due to futility and safety concerns, suggesting that CRT can worsen or provoke dyssynchrony in patients with little or no dyssynchrony [57].

EchoCRT carried this issue further by using rigorous imaging criteria to detect dyssynchrony among patients with QRS duration ≤ 130 ms, thus including those with nominally normal QRS duration (<120 ms) and those slightly higher, as well as HFrEF with LVEF $\leq 35\%$, LVED ≥ 55 mm and stable, guidelines-based pharmacological therapy [58]. Patients were randomized to CRT or no CRT. The study was stopped early due to futility, and death from cardiovascular causes was higher among patients who received CRT.

While normalizing conduction patterns alone can account for mechanical benefit, cellular and molecular alterations seem likely to contribute. Molecular mechanisms are not fully understood but, in experimental studies, CRT is associated with homogenization of stress kinase activity, potentially important in supporting contractile function, and reducing fibrosis [59].

CRT is also associated with decline in global apoptosis and enhanced cell-survival signaling [60, 61]. Biventricular pacing reduces interstitial remodeling [61]. TNF- α , which is not present in normal myocardium, stimulates fibrosis and apoptosis and contributes to the progression of heart failure by direct toxic effects [62] and is activated by mechanical stretch [63]. CRT lowers LV TNF- α after 6 months of therapy [61].

CRT also alters mitochondrial proteins [64] and upregulates β -1 receptors and adenylate cyclase activity [65] and partially ameliorates prolongation of the action potential duration (APD) selectively in the lateral wall [66].

Current AHA/ACC practice guideline* suggest application of CRT as follows [66]:

5.3.1. Class I indications:

1. CRT is indicated for patients who have LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater, and NYHA class II, III, or ambulatory IV symptoms on guideline-directed medical therapy (GDMT). (*Level of Evidence: A for NYHA class III/IV; Level of Evidence: B for NYHA class II*).

5.3.2. Class IIa indications:

1. CRT can be useful for patients who have LVEF \leq 35%, sinus rhythm, a non-LBBB pattern with a QRS duration \geq 150ms, and NYHA class III/ambulatory class IV symptoms on GDMT (*Level of Evidence: A*).
2. CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, LBBB with a QRS duration of 120–149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT (*Level of Evidence: B*).
3. CRT can be useful in patients with AF and LVEF of 35% or less on GDMT if (a) the patient requires ventricular pacing or otherwise meets CRT criteria and (b) atrioventricular nodal ablation or pharmacological rate control will allow near 100% ventricular pacing with CRT (*Level of Evidence: B*).
4. CRT can be useful for patients on GDMT who have LVEF of 35% or less and are undergoing placement of a new or replacement device implantation with anticipated requirement for significant ($>$ 40%) ventricular pacing (*Level of Evidence: C*).

5.3.3. Class IIb indications

1. CRT may be considered for patients who have LVEF of 35% or less, sinus rhythm, a non-LBBB pattern with QRS duration of 120–149 ms, and NYHA class III/ambulatory class IV on GDMT (*Level of Evidence: B*).
2. CRT may be considered for patients who have LVEF of 35% or less, sinus rhythm, a non-LBBB pattern with a QRS duration of 150 ms or greater, and NYHA class II symptoms on GDMT (*Level of Evidence: B*).
3. CRT may be considered for patients who have LVEF of 30% or less, ischemic etiology of HF, sinus rhythm, LBBB with a QRS duration of 150 ms or greater, and NYHA class I symptoms on GDMT (*Level of Evidence: C*).

*These guidelines were published before BLOCK-HF and EchoCRT were published.

Use of CRT is associated with short- and long-term adverse effects [46–58]. Most commonly reported complications include coronary-sinus dissection/perforation, lead dislodgement, implantation site infection, hemo-/pneumothorax, pericardial effusion/pericarditis, hematoma, pacing failure, atrial fibrillation, inappropriate device stimulation of tissue, and DVT.

6. The future of therapy for heart failure

Future developments for heart failure therapy will focus on the major current deficiencies. For example, heart failure with preserved ejection fraction (HFpEF) is now known to account for approximately half the heart failure population, with the same 5-year survival rate as HFrEF. No life-prolonging or hospitalization reducing therapy now exists for patients with HFpEF though there has been a suggestion of possible benefit with spironolactone [67]. However, despite early hope with calcium channel blockers, there are no therapies specifically to prevent or reverse diastolic dysfunction or to prevent or reverse fibrosis, which may be important pathophysiological underpinnings of HFpEF (though these problems may be affected by therapies aiming at other cardiac functional targets). Both problems are under active drug development but no solutions have yet emerged. With regard to fibrosis, study in valve disease models [68] suggest that collagen, by far the predominant element of myocardial fibrous tissue, may not be the most appropriate target for preventive therapy, but that noncollagen elements, which can directly affect force transmission, may be the more appropriate targets. It is not clear whether this finding in regurgitant valve diseases, in which the myocardium is responding to extrinsic loading conditions, can be extrapolated to systolic heart failure in which intrinsic metabolic abnormalities are pathophysiologically most important. Moreover, though systolic function is importantly improved by several currently available therapies, drugs that specifically improve intrinsic myocardial contractility without countervailing adverse effects still are needed. One promising candidate is omecamtiv mecarbil [69], which enhances myosin cross-bridge formation and duration, thus increasing systolic ejection time, but without increasing oxygen utilization. Others may follow. Finally, a major adjunct to the therapies, themselves, is monitoring the effects of therapy to enable precise titration and maximize benefits [70]. Although beyond the scope of this chapter, it is clear that devices for remote monitoring are gaining ever greater impact on therapeutic decisions and will continue to be developed.

7. Conclusions

Therapy for heart failure and, specifically, for systolic heart failure (HFrEF), has progressed dramatically during the past 30 years. In addition to the use of diuretics to relieve volume overloading and associated symptoms, which already was established, five different groups of drugs and multiple devices have been developed and assessed in large randomized controlled clinical trials. The most recent of these developments, an f-current blocker to slow heart rate and a neprilysin blocker to enhance blood concentrations of several vasoactive substances, have added to the benefits on survival and hospitalization achieved by previously developed drugs that are still in use. At the same time, use of some drugs that were used conventionally before recent additions has diminished (e.g., digoxin), superseded by new developments. Innovations in therapeutic devices for heart failure also have moved rapidly though, over the past 5 years, the greatest advances have been in delineation of the appropriate application of existing devices. Nonetheless, 6 million Americans have heart failure as this is written and one million of them will be hospitalized this year. Therefore, research and

development of therapeutics remain importantly needed, most particularly focused in several areas. For example, no life-prolonging therapies yet have been identified for HFpEF (which affects half the heart failure population), no therapies specifically to mitigate diastolic dysfunction are available and no therapies specifically preventing myocardial fibrosis have been developed. Moreover, though systolic function is importantly improved by several currently available therapies, drugs that specifically improve intrinsic myocardial contractility without countervailing adverse effects still are needed. Thus, while the current therapeutic landscape reveals far more effective treatments than in the past, new research and development for heart failure therapeutics are greatly needed.

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