Heart failure is a pathological condition that impairs the ability of the heart to keep up with the metabolic demands of the body and with progression results in multi-organ abnormalities and eventually death [1,2]. Reduced ejection fraction (EF) is usually defined as EF<45-50%. This can result from conditions that reduce the ability of heart to pump blood which include decreased contractility of myocardium secondary to reduced coronary perfusion, structural causes like damaged heart valves, cardiac muscle or pericardial diseases etc [3]. The mechanistic details that drive the progression of heart failure are not well understood but molecular and cellular changes point towards the role of neuro-hormonal activation and ventricular remodeling as primary determinants [4]. The sequential and progressive upregulation of renin-angiotensin aldosterone system, increased levels of norepinephrine and endothelin-1 play a significant role in the progression of LV dysfunction. Coronary artery disease (CAD), Diabetes, and Hypertension are among the leading causes whereas other factors such as genetic, alcohol abuse, infectious myocarditis, chemotherapeutic agents etc also account for significant number of cases [5,6]. The symptoms of decompensated HF are very non-specific (shortness of breath, fatigue, weakness, etc) and need evaluation in the context of the overall clinical picture, including signs like extremity edema, jugular venous distention, S3) [5,7]. Tests like BNP, ECG, CXR, echocardiography, C-MRI allow confirmation of the diagnosis [5].

HF affects about five million people in the US alone. The numbers are staggering with close to fifty percent mortality within five years of diagnosis [8]. It is the leading cause of hospitalization, and healthcare expenditures in the US with the total direct and indirect costs as high as $32 billion each year [9], which is estimated to increase to $70 billion by 2030 [10]. In fact, by 2030 an estimated 8 million people will suffer from HF in the US with direct healthcare costs of $53 billion, an increase of almost 150% from 2010 [10]. Thus, there is an urgent need for the development of new therapeutics for the treatment of heart failure.

Mechanisms of Heart Failure

Various models have been proposed to explain the mechanisms that precipitate and drive the progression of heart failure. The Renin Angiotensin system (RAS) dependent retention of excessive salt and water (cardio-renal model) [11] or abnormal pumping capacity of the heart (hemodynamic model) have been the traditional proposed models. There is usually an initial event that damages the heart muscle with resultant loss of functioning myocytes that causes decline in the pumping capacity of the heart. This decline leads to activation of a number of compensatory mechanisms including activation of the sympathetic system and the RAS [11,12]. Increased circulating norepinephrine levels lead to increased peripheral vasoconstriction, which causes elevated heart rates and augments stroke volume (Figure 1) [11]. The activation of these mechanisms does delay the onset of symptoms; however by augmenting myocardial oxygen demand, this can intensify ischemia and increase propensity for arrhythmias. Increased levels of angiotensin produced by RAS activation also promotes vasoconstriction and increases salt and water retention by increasing aldosterone levels [11]. These factors in addition to...
blunted responsiveness of kidneys to natriuretic peptides (ANP, BNP) lead to worsening of fluid retention [12,13]. In addition eNOS (endothelial nitric oxide synthase) mediated vasodilation in HF patients is blunted, which is secondary to attenuated eNOS activity [14,15]. The sustained activation of neurohormonal and cytokine systems cause a series of changes in the myocardium that have been collectively referred to as remodeling and develop generally when patients transition to symptomatic HF. Inducible NOS (iNOS) (which shows increased expression in advanced HF patients [15]) may influence pathological remodeling as transgenic mice deficient in iNOS were found to have improved survival and remodeling after an ischemic event [16,17].

Management and Treatment of Heart Failure

Although lifestyle modifications have been routinely recommended for heart disease, these interventions have not been studied in clinical trials and are based on clinician experience and routine practice. Some evidence has been put forward that aerobic exercise might benefit heart failure patients by improving the quality of life and reduce hospitalizations. In addition certain dietary therapies, such as a low sodium diet that are prescribed for heart failure patients are again based on slim evidence [18]. Chronic HF is managed by administering various medications that help increase the cardiac function by lowering the pressure overload (neuro-hormone blockers), and decrease fluid retention (diuretics).

Diuretics

Diuretics provide symptomatic relief by relieving fluid retention, with loop diuretics being the first choice in all but a few patients. Combination of loop and thiazide diuretic (in addition to an aldosterone antagonist that produces what is called sequential nephron blockade) is usually required in case of severe heart failure. Diuretic therapy may provide symptom relief but these agents have not been shown to provide mortality benefit.

ACE Inhibitors (ACEIs)

ACEIs are the first line therapy for heart failure with reduced EF. These agents prevent remodeling in addition to their effect on blood pressure and after load reduction. In patients with left ventricular systolic dysfunction, treatment with ACEIs is recommended. In clinical trials carried out with patients who have NYHA class II, III or IV HF, enalapril was shown to provide mortality benefit with relative risk reduction in death due to HF [19-21]. Enalapril was also shown to have mortality benefit over the combination of hydralazine and isosorbide dinitrate [22,23]. Angiotensin receptor blockers (ARBs) have also been shown to
be equally efficacious as ACEI in the treatment of HF and appear to provide the same mortality benefit as ACEIs [24]. This was demonstrated in a study where valsartan and candesartan were found to decrease cardiovascular mortality by 16% and readmission rate by 17-22% [25].

**Beta-blockers**

Beta-blockers are the mainstay of initial treatment for heart failure with systolic dysfunction as these agents are very important disease modifying drugs. By reducing metabolic demand, beta-blockers cause reduction in symptoms and improve systolic function with resultant increase in EF. Beta-blocker therapy in RCT’s was found to reduce mortality by 34% in conjunction with optimal HF therapy [26]. Only bisoprolol, carvedilol and metoprolol succinate have been extensively studied and shown to have mortality benefits in all classes of heart failure [26-30].

**Additional drug therapies**

In NYHA class III & IV, aldosterone antagonists have been shown to have survival benefit [31], particularly in patients who remain symptomatic despite treatment with diuretics, ACEI, and beta-blocker. In black patients, trials comparing the use of enalapril and the combination of hydralazine and isosorbide dinitrate showed that the patients responded much better to the combinatorial therapy.

**Mechanical devices**

Ventricular arrhythmias are the leading cause of death in patients with systolic heart failure, and implantable cardioverter-defibrillators (ICDs) have been shown to reduce the risk of sudden death in patients with severe LV systolic dysfunction [32,33]. Patients with class II or III HF with EF ≤35% who have life expectancy ≥ 1 year have indication for ICD as primary prevention and in patients who survive an unprovoked episode of ventricular fibrillation or sustained ventricular tachycardia as secondary prevention [32]. In patients who meet the following criteria—Class III-IV heart failure, ejection fraction ≤35% and QRS duration of 120 ms or more—cardiac-resynchronization therapy (CRT) has been shown to be beneficial [34,35]. The synchronization of atrial and biventricular pacing improved cardiac function and resultant symptom improvement and functional capacity [35-37]. This was demonstrated in a retrospective analysis of patients with class IV symptoms, showing an increase of 45 m in the 6 minute walk distance, a 25 point improvement in the Minnesota Living with Heart Failure score, and reduction by at least one NYHA functional class in 78% of the patients. Outcomes in advanced systolic heart failure have improved with the use of medical and device therapies (as discussed above) but eventual progression of the disease requires pursuance of more radical approaches. Ionotropic and advanced therapies may support the clinical status in the short term but long term survival is difficult to achieve on these therapies [38,39]. The advent of newer continuous flow Left Ventricular Assist Devices (LVAD) have made these devices a more viable options as a bridge to transplantation [40,41]. Older pulsatile devices were associated with more incidence of infections, bleeding, stroke, and device failures that required repairing or replacing the device [42]. Continuous flow devices have been proven to be more effective as compared to older devices and have been shown in trials to improve survival to the extent newer devices are being offered as destination therapies [43]. In a trial comparing continuous flow devices vs older pulsatile devices, newer devices were found to significantly improve probability of survival from stroke and device failure at 2 years in advanced heart failure patients [40].

In patients who are considered refractory to therapy, heart transplantation is usually the last resort [44]. Given the difficulty in obtaining suitable donor organs, patients have to meet very specific criteria, and they also should be able to withstand surgery in addition to intensive medical therapies after the transplant [45,46].

**New mechanisms involved in heart failure**

Even though the current medications have somewhat improved survival in HF patients, the continued high mortality rate and lack of development of new drugs in the last two decades has necessitated the development of new therapies. The neuro-humoral model might explain some aspects of the disease progression seen in the failing heart, but other models have been put forth that can explain some of the mechanistic details that drive pathological remodeling of the myocardium [4]. There have been studies that have proposed promising pathways that can be exploited as new therapies for treating HF Members of the bromodomain and extraterminal (BET), a family of epigenetic reader proteins, have been shown to be critical mediators of pathologic cardiac hypertrophy and HF pathogenesis [47,48]. In a recent study, the authors used a well-known specific inhibitor of BET, called JQ1, in the mouse model of pressure overload and they found out that the targets of BET overlap with the pattern in human diseased hearts, supporting the notion that BET inhibition may subserve a novel therapeutic approach in heart failure [47]. In another recent study, it was demonstrated that mice with chronic PDE9A (phosphodiesterase 9A) inhibition exhibited reversal of pre-established hypertrophy in a nitric oxide-independent manner [49]. The same study also showed an upregulated expression of PDE9A not only in left ventricular hypertrophy in humans but also in heart failure with preserved ejection fraction [49]. Therefore, developing a therapy targeted targeting PDE9A inhibition may be considered a promising treatment for HF patients. Collectively, these novel findings clearly point towards exploration of new therapeutic approaches for heart failure.

**Recent FDA approvals for heart failure drugs**

Recent approval of more HF drugs by FDA is promising. LCZ696, a combination of two blood pressure lowering drugs valsartan and sacubitril, is an investigational drug that was recently tested in patients with systolic heart failure [50]. FDA has granted a priority review to LCZ696 which could expedite development process and market availability of the drug. Also, ivabradine was approved by FDA for patients with higher risk of hospitalization due to chronic worsening HF [51]. It was shown to reduce cardiovascular death by 18% and significantly reduce
the risk of hospitalization due to heart failure exacerbation as compared to placebo [52].

Conclusion

Diverse underlying mechanisms for HF and other complications such as diabetes, obesity and lifestyle make developing effective therapies challenging. However, recent discoveries of novel pathways and drug development have increased our understanding about both the pathogenesis of the disease and the pathways to be exploited.

References

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, et al. (2013) 2013 acc/aha guideline for the management of heart failure: A report of the american college of cardiology foundation/americ

2. Jessup M (1988) Managing congestive heart failure. Geriatrics 43(11): 35-39, 42.

3. Cleland JG, Torabi A, Khan NK (2005) Epidemiology and management of heart failure and left ventricular systolic dysfunction in the aftermath of a myocardial infarction. Heart 91(Suppl 2): 87-813.

4. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN (1984) The neurohumoral axis in congestive heart failure. Ann Intern Med 101(3): 370-377.

5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, et al. (2013) 2013 acc/aha guideline for the management of heart failure: Executive summary: A report of the american college of cardiology foundation/americ

6. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, et al. (2009) 2009 focused update incorporated into the acc/aha 2005 guidelines for the diagnosis and management of heart failure in adults a report of the american college of cardiology foundation/americ

7. Tcece MA, Pennington JA, Segal BL, Jessup M (1999) Heart failure: Clinical implications of systolic and diastolic dysfunction. Geriatrics 54(8): 24-28, 31-23.

8. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, et al. (2014) Heart disease and stroke statistics-2014 update: A report from the american heart association. Circulation 129(3): e28-e292.

9. Heidenreich PA, Tngdlon JG, Khavjou OA, Butler J, Dracup K, et al. (2011) Forecasting the future of cardiovascular disease in the united states: A policy statement from the american heart association. Circulation 123(8): 933-944.

10. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, et al. (2013) Forecasting the impact of heart failure in the united states: A policy statement from the american heart association. Circ Heart Fail 6(3): 606-619.

11. Kjaer A, Hesse B (2001) Heart failure and neuroendocrine activation: Diagnostic, prognostic and therapeutic perspectives. Clin Physiol 21(6): 661-672.

12. Pieruzzi F, Abassi ZA, Keiser HR (1995) Expression of renin-

13. Gupta D, Georgiopoulou VV, Kalogeropoulos AP, Dunbar SB, Reilly CM, et al. (2012) Dietary sodium intake in heart failure. Circulation 126(4): 479-485.

14. Jones SP, Greer JM, van Haperen R, Duncker DJ, de Crom R, et al. (2003) Endothelial nitric oxide synthase overexpression attenuates congestive heart failure in mice. Proc Natl Acad Sci 100(8): 4891-4896.

15. Drexler H (1999) Nitric oxide synthases in the failing human heart: A doubled-edged sword? Circulation 99(23): 2972-2975.

16. Jones SP, Bolli R (2006) The ubiquitous role of nitric oxide in cardioprotection. J Mol Cell Cardiol 40(1): 16-23.

17. Zhang P, Xu X, Hu X, van Deel ED, Zhu G, et al. (2007) Inducible nitric oxide synthase deficiency protects the heart from systolic overload–induced ventricular hypertrophy and congestive heart failure. Circ Res 100(7): 1089-1098.

18. Merrill AJ (1949) Mechanisms of salt and water retention in heart failure. Am J Med 6(3): 357-367.

19. Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative north scandinavian enalapril survival study (consensus). The CONSENSUS Trial Study Group (1987). N Engl J Med 316(23): 1429-1435.

20. Swedberg K, Enero P, Kjekshus J, Snapinn S (1990) Effects of enalapril and neuroendocrine activation on prognosis in severe congestive heart failure (followup of the consensus trial). Am J Cardiol 66(11): D40-D45.

21. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure (1993). Lancet 342(8875): 821-828.

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

23. Loeb HS, Johnson G, Henrick A, Smith R, Welson J, et al. (1993) Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with congestive heart failure. The v-kept v cooperative studies group. Circulation 87: V178-V187.

24. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komaja M, et al. (2009) Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (hheaal study): A randomised, double-blind trial. Lancet 374(9704): 1840-1848.

25. McMurray JJ, Östergren J, Swedberg K, Granger CB, Held P, et al. (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: The charm-added enzyme: The charm-added trial. Lancet 362(9366): 767-771.

26. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, et al. (2003) Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the carvedilol or metoprolol european trial (comet): Randomised controlled trial. Lancet 362(9777): 7-13.

27. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, et al. (2001) Effect of carvedilol on survival in severe chronic heart failure. N
Current and Future Therapies for Management of Systolic Heart Failure

28. Packer M, Colucci WS, Sackner-Bernstein JD, Liang C-s, Goldscher DA, et al. (1996) Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure the precise trial. Circulation 94(11): 2793-2799.

29. Effect of metoprolol cr/xd in chronic heart failure: Metoprolol cr/xd randomised intervention trial in congestive heart failure (merit-hf) (1999). Lancet 353(9169): 2001-2007.

30. The cardiac insufficiency bisoprolol study ii (cibis-ii): A randomised trial (1999). Lancet 353(9146): 9-13.

31. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, et al. (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 341(10): 707-717.

32. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, et al. (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 346(12): 877-883.

33. Goldenberg I, Moss AJ, Hall WJ, McNitt S, Zareba W, et al. (2006) Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the multicenter automatic defibrillator implantation trial ii. Circulation 113(24): 2810-2817.

34. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, et al. (2012) Esc guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail 14(8): 803-869.

35. Yu C-M, Chau E, Sanderson JE, Fun K, Tang MO, et al. (2002) Tissue doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 105(4): 438-445.

36. Quo Q, Chen Y-x, Mai J-t, Yuan W-l, Wei Y-l, et al. (2015) Effects of cardiac resynchronization therapy on left ventricular remodeling and dyssynchrony in patients with left ventricular noncompaction and heart failure. Int J Cardiovasc Imaging 31(2): 329-337.

37. Yu C-M, Fung W-H, Lin H, Zhang Q, Sanderson JE, et al. (2003) Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol 91(6): 684-688.

38. Nielsen DV, Algotsson L (2015) Outcome of inotropic therapy: Is fewer always more? Curr Opin Anaesthesiol 28(2): 159-164.

39. Teerlink JR, Alburikan K, Metra M, Rodgers J (2015) Acute decompensated heart failure update. Curr Cardiol Rev 11(1): 53-62.

40. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, et al. (2009) Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 361(23): 2241-2251.

41. Rose EA, Gelijns AC, Moskowitz AJ, Hetjans DF, Stevenson LW, et al. (2001) Long-term use of a left ventricular assist device for end-stage heart failure N Engl J Med 345(20): 1435-1443.

42. Boyle AJ, Russell SD, Teuteberg JJ, Slaughter MS, Moazami N, et al. (2009) Low thromboembolism and pump thrombosis with the heartmate ii left ventricular assist device: Analysis of outpatient anti-coagulation. J Heart Lung Transplant 28(9): 881-887.

43. Anand J, Singh SK, Hernández R, Parnis SM, Civitello AB, et al. (2015) Continuous-flow ventricular assist device exchange is safe and effective in prolonging support time in patients with end-stage heart failure. J Thorac Cardiovasc Surg 149(1): 267-278.

44. Costanzo MR, Augustine S, Bourge R, Bristow M, O’Connell JB, et al. (1995) Selection and treatment of candidates for heart transplantation: A statement for health professionals from the committee on heart failure and cardiac transplantation of the council on clinical cardiology, american heart association. Circulation 92(12): 3593-3612.

45. Dew MA, Kormos RL, Roth LH, Murali S, DiMartini A, et al. (1999) Early post-transplant medical compliance and mental health predict physical morbidity and mortality one to three years after heart transplantation. J Heart Lung Transplant 18(16): 549-562.

46. Dreyfus G, Jebra V, Mihalikam S, Carpenter AF (1991) Total orthotopic heart transplantation: An alternative to the standard technique. Ann Thorac Surg 52(5): 1181-1184.

47. Anand P, Brown JD, Lin CY, Qi J, Zhang R, et al. (2013) Bet bromodomains mediate transcriptional pause release in heart failure. Cell 154(3): 569-582.

48. Spiltoir Jl, Stratton MS, Cavasin MA, Demos-Davies K, Reid BG, et al. (2013) Bet acetyl-lysine binding proteins control pathological cardiac hypertrophy. J Mol Cell Cardiol 63: 175-179.

49. Lee DI, Zhu G, Sasaki T, Cho GS, Hamdani N, et al. (2015) Phosphodiesterase 9a controls nitric-oxide-independent cGMP and hypertrophic heart disease. Nature 519(7544): 472-476.

50. Jessup M (2014) Neprilysin inhibition—a novel therapy for heart failure. N Engl J Med 371(11): 1062-1064.

51. Fox K, Ford I, Steg PG, Tendera M, Ferrari R (2008) Ixabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (beautiful): A randomised, double-blind, placebo-controlled trial. Lancet 372(9641): 807-816.

52. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, et al. (2010) Ixabradine and outcomes in chronic heart failure (shift): A randomised placebo-controlled study. Lancet 376(9744): 875-885.