Published in final edited form as:

Heart Fail Clin. 2020 October ; 16(4): 441–456. doi:10.1016/j.hfc.2020.06.005.

Addressing Comorbidities in Heart Failure: Hypertension, Atrial Fibrillation, and Diabetes

Aakash Bavishi, MD⁽¹⁾, Ravi B. Patel, MD⁽¹⁾

⁽¹⁾Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

Keywords

heart failure; prevalence; diabetes mellitus; atrial fibrillation; hypertension

Introduction

Heart failure (HF) currently affects 6.2 million adults in the United States (US) and is associated with a substantial burden to the healthcare system, with direct annual cost of \$11 billion in 2014.^{1,2} Alarming, projections indicate that by the year 2030, 8 million people in the US will have HF, with direct costs expected to surpass 53 billion dollars.^{1,3} Similar concerning trends are evident worldwide, as the global prevalence of HF is estimated to be 26 million and rising.⁴ The increasing prevalence of HF cannot be fully attributed to a rising incidence, as HF incidence has remained relatively stable due to substantial improvements in prevention and treatment of acute coronary syndromes.^{4–6} An aging population, coupled with advancements in HF management, are likely key contributors to the rising prevalence of HF as more individuals are now living with HF. Furthermore, there has been a temporal increase in the proportion of patients with heart failure with preserved ejection fraction (HFpEF) as the population ages. Due to growth of the HF population and shift in its makeup to include a higher proportion of elderly individuals with HFpEF, the accumulation of comorbidities is common, and represents an additional clinical challenge in providing optimal care in HF. Several comorbidities, including hypertension (HTN), atrial fibrillation (AF), and diabetes mellitus (DM), are not only commonly associated with HF, but also may be linked to worse clinical outcomes.^{7,8,9} Thus, optimal management of these comorbidities is paramount. In this review, we describe the HF-specific epidemiology, management strategies, and future directions of research in these 3 disease states.

Address for Correspondence: Ravi B. Patel MD, Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, 676 N. St Clair St, Suite 600, Chicago IL, 60611; Tel: (312) 503-5779; Fax: (312) 695-0063; ravi.patel@northwestern.edu; Twitter: @RBPatelMD.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures:

Dr. Aakash Bavishi has nothing to disclose.

Hypertension

Epidemiology

According to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) definition, over 103 million individuals in the US are burdened with HTN.^{10,11} While the age-standardized prevalence of HTN has decreased, the absolute HTN burden in the US has increased.¹² In 2010, the global prevalence of HTN was 1.4 billion people with projections that prevalence will exceed 1.6 billion people by 2025.¹³

HTN and HF are inextricably linked. Of 5,143 patients in the Framingham Heart Study, HTN preceded the development of HF in 91% of all newly diagnosed HF patients over the course of 20 years of follow-up.^{14,15} Hypertensive men and women are at 2-fold and 3-fold increased risk of developing HF, respectively, compared with normotensive subjects.⁷

Important racial disparities exist in prevalence and management of HTN. African Americans in the US are more likely to have HTN compared to other ethnic groups and are less likely to reach target blood pressure goal.^{16–18} The disproportionate prevalence of HTN in African Americans is directly associated with higher rates of incident HF in this racial group.^{19,20}

Management of Hypertension in HF

The ACC/AHA stage-wide classification of HF includes 4 categories of HF based on the presence or absence of risk factors, structural heart disease, or HF symptoms.²¹ Stage A represents those with risk factors for HF, Stage B indicates the presence of structural heart disease, Stage C represents those with prior or current HF symptoms and Stage D indicates refractory HF. This schema is useful to guide HTN management in patients at risk for HF or with prevalent HF. Across all strata of HF, lifestyle counseling regarding diet, weight loss, exercise, smoking cessation, and alcohol moderation is strongly recommended.²² Current guidelines additionally recommend treatment of blood pressure (BP) to less than 130/80 mmHg among those at increased risk for HF (Stage A) based on the results of Systolic Blood Pressure Intervention Trial (SPRINT), which demonstrated a reduction in incidence of HF among trial participants treated to this target.^{21,23} In general, the optimal blood pressure target for the treatment of HTN in the setting of clinically manifest HF has not been well established. Current guidelines have extended the recommendation of systolic BP <130 mmHg to those patients with Stage C HF, regardless of ejection fraction.²¹ These recommendations are primarily based on the results of the SPRINT trial, with the acknowledgement that this evidence was not specifically generated from patients with prevalent HF. Detailed approaches to HTN management in HF, including the choice of specific pharmacologic agents, are displayed in Table 1 and Figure 1. Table 1 depicts an approach to HTN management based on ACC/AHA Stage of HF. A generalized approach to hypertension management in HF patients is additionally shown in Figure 1.

Future Directions

Further investigation is required to determine the ideal BP target among those patients with Stage C HF, regardless of ejection fraction. This is particularly important given the apparent paradox between BP and prognosis once HF with reduced ejection fraction (HFrEF) is

present. Specifically, despite the association of BP with incident HF, lower BP is associated with worse prognosis in the setting of overt HFrEF.²⁴

Additionally, further clarification regarding the utility of specific anti-hypertensive therapies in preventing HF among those at higher risk is warranted. Indeed, chlorthalidone was associated with reduction in HF risk as compared with amlodipine in the Anti-Hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial.²⁵ The anti-hypertensive effect of sacubitril-valsartan, an angiotensin receptor neprilysin inhibitor (ARNI), is stronger than angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors alone, and thus raise the possibility that this agent may also be particularly effective in curbing HF risk among those at high risk.

Regardless of the approach, it is becoming increasingly clear that a team-based, collaborative approach to managing HTN is of benefit to the HF patient.²⁶ Collaboration between nephrologists, cardiologists, and internists to create a personalized treatment strategy to which patients can easily adhere is critical. Collaboration between physicians, pharmacist, mid-level providers, and social workers is essential to create more opportunities for lifestyle and medication interventions and address economic and social barriers to care. Several technological innovations such as text message reminders and mobile app notifications have shown promise in improving medication adherence and may have an important role in the comprehensive treatment plan for hypertensive patients.^{27–29} Additionally, HTN management is based upon the same principle as guideline-directed medical therapy in HFrEF: the timely initiation and titration of pharmacotherapy to goal doses. As such, frequent visits with various members of the medical team, including HF nurse practitioners, may be particularly important to reach target BP goals in HF.

Atrial Fibrillation

Epidemiology

Current estimations demonstrate that between 2.7 to 6.1 million people in the US have AF and over 33.5 million individuals worldwide are burdened by AF.^{10,30} There has been a consistent increase in the incidence and prevalence of AF, as AF is predicted to affect 6–12 million people in the US by 2050 and 17.9 million in Europe by 2060.^{31,32,33,34} This increased incidence and prevalence has been attributed to both increases in prevalence of risk factors for AF (i.e., DM and obesity) as well as the heightened awareness and detection of AF.^{31,35,36}

Up to 62% of individuals with HF may have AF at some point during their life course.³⁷ Indeed, AF and HF share several common, underlying risk factors. There appears to be a bidirectional relationship between these 2 disease states, in which each disease induces inflammatory, neurohormonal, and structural changes that predisposes to the other syndrome.³⁸ Additionally, numerous studies have demonstrated that patients with both AF and HF have worse short term and long term outcomes than either condition alone.^{8,39–41}

Management of AF in Patients with HF

The approach to management of AF in HF patients depends on several factors including the acuity of each condition, degree of HF decompensation, left ventricular function, and presence of other structural heart abnormalities (Figure 2).

In the setting of acute decompensated HF with concomitant AF and rapid ventricular rate, primary clinical goals should be decongestion and consideration of agents to carefully lower ventricular rate. Caution should be taken in aggressive rate control in the setting of acute HF, as patients with significantly decompensated HF may not tolerate a sudden decrement in ventricular rate. In patients with HFrEF, non-dihydropyridine calcium channel blockers should be avoided. Amiodarone and digoxin may be appropriate therapies in the acute setting until patients are decongested and can tolerate titration of β blocker therapy. In patients with HFpEF, non-dihydropyridine calcium channel blockers or β blockers may be useful to acutely control heart rate. If AF is determined to be the true trigger for HF decompensation, an acute rhythm control strategy can also be pursued. The optimal timing of rhythm control of AF via cardioversion during the course of hospitalization for HF is not well understood.

In the non-acute setting, the decision whether to pursue a rate or rhythm control strategy is multi-faceted and should be based on careful discussions with patients regarding risks and benefits, along with assessment of ejection fraction (Figure 2). Symptomatic AF may influence the decision to pursue a rhythm controlling strategy in the setting of HF. However, the degree to which AF contributes to symptoms such as dyspnea or fatigue in patients with HF and AF is especially challenging. First, the constellation of symptoms in AF and HF are overlapping and may be difficult to distinguish. Indeed, dyspnea and non-specific fatigue are hallmarks of both syndromes. Additionally, inactive lifestyle and functional limitations due to HF may mask symptomatic AF, which may only be manifest at higher ventricular rates.

There is limited efficacy of anti-arrhythmic drug (AAD) therapy for rhythm control in the setting of AF and HF. The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial did not demonstrate a significant reduction in cardiovascular mortality with rhythm control compared with rate control among patients with HFrEF.⁴² Additionally, the Danish Investigators of Arrhythmia Mortality on Dofetilide in Congestive Heart Failure (DIAMOND-CHF) trial, which compared dofetilide to placebo in HFrEF, failed to show an improvement in mortality. However, a reduction in hospitalizations was noted in the dofetilide arm in DIAMOND-CHF.⁴³

The limited efficacy of AAD led to speculation that maintenance of sinus rhythm through catheter ablation (CA) may be more beneficial to patients with HF compared with AAD alone. In HFrEF, several small studies have shown improvement in exercise capacity, quality of life metrics, and left ventricular function with CA, although data regarding clinical cardiovascular outcomes are limited.^{44–48} A small multicenter randomized study showed the superior efficacy of CA compared to amiodarone in reducing unplanned hospitalizations and mortality in HFrEF patients.⁴⁹ Subsequently, results from the recent Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial demonstrated that in patients with AF and

symptomatic HFrEF (LVEF $\leq$ 35%), CA was associated with a significant reduction in death and hospitalization for HF, greater improvement in LVEF, and long-term maintenance of sinus rhythm.⁵⁰ Significant questions remain about generalizability of CASTLE-AF findings given the highly selected patient population and exclusion of those patients who easily achieved rhythm control.⁵⁰ The results of this study were reflected in the 2019 update to the 2014 AHA/ACC/Heart Rhythm Society Guidelines for AF management, which stated that CA may be reasonable in selected HFrEF patients to potentially lower mortality rate and reduce hospitalization for HF (Class IIB recommendation).⁵¹

Despite the prevalence and significant adverse effects of AF in HFpEF, data is even more limited with regard to management of AF in this vulnerable population.^{52,53} Aggressive management of obstructive sleep apnea, obesity, and DM should be pursued, which has been shown to reduce AF recurrence and improve cardiorespiratory fitness in HFpEF.^{54–57} Observational studies have demonstrated associations of rhythm control of AF with improved quality of life, functional capacity, and lower all-cause mortality in HFpEF.^{58,59} However, randomized clinical trial evidence is currently lacking. Similar to management of AF in all HF patients, a comprehensive patient-specific evaluation – including careful symptom assessment, cardiac monitoring to assess efficacy of rate control, and patient preference – is needed to determine AF treatment strategy. In specific patient populations, such as restrictive cardiomyopathy or hypertrophic cardiomyopathy in which the atrial contractile function is critical to hemodynamics, aggressive strategies for rhythm control should be pursued. In patients whom AF is thought to be driving frequent HF hospitalizations, a more aggressive rhythm control strategy should be pursued.

Finally, in the absence of compelling contraindications, all patients should be anticoagulated regardless of left ventricular ejection fraction.⁶⁰ Multiple large meta-analyses have confirmed the efficacy and safety of non-vitamin K antagonist oral anticoagulants in patients with AF and HF.^{61,62}

Due to current gaps in evidence, there is no widely-accepted treatment pathway for the management of AF in HF. As such, we provide a general approach to comprehensive management of AF in HF in Figure 2.

Future Directions

Significant research is still needed to define optimal AF management strategies in HF. In the setting of HFrEF, additional clinical trials of CA, inclusive of broader populations and of larger sample size, are necessary to confirm the suggested benefits of CA noted in the CASTLE-AF trial. Identification of HFrEF patients who are most likely to benefit from upfront CA without an initial trial of AAD therapy may also be important to further understand.

There is currently a lack of evidence for CA in the setting of HFpEF. While an intention to treat analysis of the recent Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial demonstrated a decrease in mortality, stroke, and cardiac arrest in HF patients undergoing CA compared to medical therapy (rate or rhythm control), characterization of HF by ejection fraction status was not fully captured in this analysis.⁶³

Given the frequent coexistence of AF and HFpEF and the association of AF with worse long-term outcomes, trial-level evidence for treatment of AF in HFpEF represents a critical unmet need.

Further research is also needed to identify which patients would benefit from CA compared with invasive rate control through atrioventricular (AV) nodal ablation with pacing. The Pulmonary Vein Antrum Isolation vs. AV Node Ablation with Bi-Ventricular Pacing for Treatment of AF in Patients with Congestive HF (PABA-CHF) demonstrated improvement in quality of life, left ventricular (LV) function and 6 minute walk test at 6 months in patients undergoing pulmonary vein isolation compared to patients undergoing AV nodal ablation with biventricular pacing.⁶⁴ However, this study was limited in sample size and duration (6 months). The effect of AV nodal ablation and pacing compared with CA is being further investigated in the Rhythm Control-Catheter Ablation With or Without Anti-Arrhythmic Drug Control of Maintaining Sinus Rhythm Versus Rate Control with Medical Therapy and/or Atrio-ventricular Junction Ablation and Pacemaker Treatment for Atrial Fibrillation (RAFT-AF) clinical trial ([NCT01420393](#)), which will include both HFrEF and HFpEF patients with New York Heart Association Class II or III symptoms.

Diabetes Mellitus

Epidemiology

In recent decades, the prevalence of DM has increased both globally and within the US. Worldwide, the prevalence of DM rose from 180 million in 1980 to 422 million in October 2014.⁶⁵ There were 30.3 million Americans with diabetes in 2015 and 2030 projections estimate 54.9 million Americans will have DM with total costs expected to surpass \$622 billion.^{66,67} Given the relatively stable incidence, the increasing prevalence of DM is due to a combination of an aging population, rise in obesity, dramatic increase in DM cases in children and adolescents, and improved medical care prolonging life in diabetic patients.⁶⁷

DM and HF commonly coexist, as rates of DM are as high as 47% in HF cohorts.^{68–71} Individuals with DM are at a 2 to 4 times increased risk of developing HF, with higher risks in women and younger adults.^{68,72} Several mechanisms underlie the increased HF risk in patients with DM, including 1) myocardial ischemia and infarction in setting of accelerated atherosclerosis; 2) fibrosis with myocardial stiffness due to advanced glycosylation end products; 3) oxidative stress; 4) autonomic dysfunction; 5) upregulation of the renin-angiotensin system; and 6) defects at cardiomyocyte level in contraction and relaxation.⁷³ Patients with HF who have DM have more frequent HF hospitalizations, lower quality of life, and higher mortality than HF patients without DM.^{9,74,75,76}

Management of DM in HF

Since the 2008 Food and Drug Administration mandate that cardiovascular safety be established among all new glucose lowering therapies, there have been numerous, large-scale clinical trials evaluating the effect of various anti-diabetic drugs on cardiovascular outcomes. This inundation of outcomes trials has revealed important insights into specific cardiovascular benefits of certain glucose-lowering therapies in the setting of HF. A

summary of anti-hyperglycemic agents and their impact on HF outcomes is shown in Table 2. The aggregate data have demonstrated a consistent benefit of sodium-glucose cotransporter 2 (SGLT2) inhibitors in reducing HF hospitalizations among patients with diabetes at moderate to high baseline cardiovascular risk. While another class of drugs, glucagon-like peptide-1 receptor agonists, has also demonstrated cardiovascular risk reduction, such effects do not seem to be driven by a reduction in HF events. More recently, a specific SGLT2 inhibitor, dapagliflozin, demonstrated substantial reductions in cardiovascular mortality and HF hospitalizations among those with HFrEF regardless of diabetes status in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial.⁷⁷ As such, SGLT2 inhibitors will likely represent the newest disease modifying therapy in HFrEF. In the setting of HFrEF in particular, this drug class should be considered a first-line therapy, regardless of diabetes status.

Among diabetic patients at risk for HF, the first-line glucose-lowering therapy is currently controversial. Given the consistent benefit of SGLT2 inhibitors in reducing cardiovascular mortality or HF hospitalization in this population, some medical societies have recommended concurrent consideration of SGLT2 inhibitors with metformin initiation.⁷⁸ Currently, according to the American Diabetes Association (ADA), metformin is still considered the first-line diabetic regimen in all patients, and has been proven to be safe in HF patients without significant chronic kidney disease.⁷⁹

In patients with HF, we have proposed an algorithm for selection of glucose-lowering therapies (Figure 3). Several factors must be accounted for when selecting proper anti-hyperglycemic agents for patients with HF, including kidney function, medication interactions, burden of polypharmacy, risk of hypoglycemia, and concurrent cardiac and non-cardiac comorbidities (Table 2). In general, given the signal of benefit from the SGLT2 inhibitor class across major cardiovascular outcome trials in reducing HF hospitalizations, we favor timely initiation of this therapeutic class, regardless of ejection fraction.

Of note, there is no current data supporting intensive hyperglycemic control in DM patients to reduce risk of incident HF.⁸⁰ The association between HbA_{1c} and HF mortality is generally U-shaped, with a nadir of risk at HbA_{1c} 7–8%.^{81,82} Indeed, HbA_{1c} reductions in large-scale outcomes trials of anti-diabetic drugs have been modest, and HF benefits are in general felt to be independent of degree of HbA_{1c} reduction.⁷⁰

Future Directions

The dogma that metformin is the foundational, first therapy for all diabetics may come under scrutiny in the future. Indeed, in HFrEF, one may argue that SGLT2 inhibitors should be the first-line therapy for cardiovascular risk reduction in light of the DAPA-HF trial. Across the spectrum of new diabetes, the efficacy of metformin as a first line therapy will be evaluated in the SGLT2 Inhibitor or Metformin as Standard Treatment of Early Stage Type 2 Diabetes (SMARTTEST) trial, which will randomize over 4000 new diabetics to metformin or dapagliflozin ([NCT03982381](#)).

The efficacy of SGLT2 inhibitors in reducing cardiovascular outcomes in the setting of HFpEF is currently being evaluated in several randomized clinical trials ([NCT03057951](#);

NCT03619213; NCT03030235). Given the natriuretic effect of SGLT2 inhibitors and robust clinical benefit of dapagliflozin in HFrEF, there remains substantial promise of this therapeutic class in the HFpEF cohort.

The growing burden of DM and associated high rates of cardiovascular comorbidities highlights the necessity of a comprehensive, multi-specialty team, which is inclusive of cardiologists, to address diabetes care. Despite the growing evidence of SGLT2 inhibitors and GLP-1 RA as cardiovascular risk-reducing agents, approximately 90% of diabetes care is restricted to primary care physicians and endocrinologists.^{83,84} However, access to endocrinologists for diabetes lags behind access to cardiologists, with disparities especially prominent in certain geographic regions.⁸⁵ Indeed, patients with diabetes at high cardiovascular risk encounter cardiologists far more frequently than endocrinologists.⁸⁶ Given the density of cardiologists and frequency of cardiology encounters, it is imperative that cardiologists take a more active role in the management of DM, including the prescription of new evidence-based glucose-lowering therapies. Such involvement by cardiologists requires familiarity with drug dosing, side effects, and appropriate patient counseling. Importantly, close communication between all members of the patient's care team, including primary care physician, endocrinologist, nephrologist, and cardiologist, is important to inform appropriate and safe diabetes treatment plans.

Conclusion

HF represents a growing burden on healthcare systems in the US and worldwide. In this review, we address 3 comorbidities inextricably associated with HF: HTN, AF, and DM. Timely identification and management of these 3 comorbidities is paramount across the spectrum of HF, from Stage A HF to end-stage cardiomyopathy. Due to the aging HF population and increasing proportion of HFpEF patients, management of HF comorbidities is increasingly complex. However, comorbidity management remains integral in optimizing long-term outcomes. Comorbidity management in HF requires close collaboration between providers and formulation of therapeutic plans that are consistent with patient values and preferences. While excitement behind new therapeutics is warranted, implementation of lifestyle modifications and relief of socioeconomic barriers to healthcare remain a critical point of emphasis for physicians. Through concerted efforts across these mechanisms, comorbidity management has promise in further improving quality of life and clinical outcomes in chronic HF.

Acknowledgments

Dr. Ravi B. Patel is supported by the NHLBI T32 postdoctoral training grant (T32HL069771).

References

1. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States. *Circulation Heart failure*. 2013;6(3):606–619. [PubMed: 23616602]
2. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National Burden of Heart Failure Events in the United States, 2006 to 2014. *Circulation: Heart Failure*. 2018;11(12):e004873. [PubMed: 30562099]

3. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. 2019;139(10):e56–e528. [PubMed: 30700139]
4. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Cardiac failure review*. 2017;3(1):7–11. [PubMed: 28785469]
5. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347(18):1397–1402. [PubMed: 12409541]
6. Najafi F, Jamrozik K, Dobson AJ. Understanding the ‘epidemic of heart failure’: a systematic review of trends in determinants of heart failure. *Eur J Heart Fail*. 2009;11(5):472–479. [PubMed: 19251729]
7. Butler J, Kalogeropoulos AP, Georgiopoulou VV, et al. Systolic blood pressure and incident heart failure in the elderly. The Cardiovascular Health Study and the Health, Ageing and Body Composition Study. *Heart (British Cardiac Society)*. 2011;97(16):1304–1311. [PubMed: 21636845]
8. Khazanie P, Liang L, Qualls LG, et al. Outcomes of medicare beneficiaries with heart failure and atrial fibrillation. *JACC Heart Fail*. 2014;2(1):41–48. [PubMed: 24622118]
9. Allen LA, Gheorghiade M, Reid KJ, et al. Identifying patients hospitalized with heart failure at risk for unfavorable future quality of life. *Circulation Cardiovascular quality and outcomes*. 2011;4(4):389–398. [PubMed: 21693723]
10. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation*. 2018;137(12):e67. [PubMed: 29386200]
11. Muntner P, Carey RM, Gidding S, et al. Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. *Circulation*. 2018;137(2):109–118. [PubMed: 29133599]
12. Dorans KS, Mills KT, Liu Y, He J. Trends in prevalence and control of hypertension according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline. *Journal of the American Heart Association*. 2018;7(11):e008888. [PubMed: 29858369]
13. Mills KT, Bundy JD, Kelly TN, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. *Circulation*. 2016;134(6):441–450. [PubMed: 27502908]
14. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *Jama*. 1996;275(20):1557–1562. [PubMed: 8622246]
15. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. *JACC: Heart Failure*. 2017;5(8):543–551. [PubMed: 28711447]
16. Hertz RP, Unger AN, Cornell JA, Saunders E. Racial disparities in hypertension prevalence, awareness, and management. *Archives of internal medicine*. 2005;165(18):2098–2104. [PubMed: 16216999]
17. Yoon SS, Carroll MD, Fryar CD. Hypertension Prevalence and Control Among Adults: United States, 2011–2014. *NCHS Data Brief*. 2015(220):1–8.
18. Lackland DT. Racial differences in hypertension: implications for high blood pressure management. *Am J Med Sci*. 2014;348(2):135–138. [PubMed: 24983758]
19. Bahrami H, Kronmal R, Bluemke DA, et al. Differences in the incidence of congestive heart failure by ethnicity: the multi-ethnic study of atherosclerosis. *Archives of internal medicine*. 2008;168(19):2138–2145. [PubMed: 18955644]
20. Bibbins-Domingo K, Pletcher MJ, Lin F, et al. Racial differences in incident heart failure among young adults. *The New England journal of medicine*. 2009;360(12):1179–1190. [PubMed: 19297571]
21. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Journal of the American College of Cardiology*. 2017;70(6):776–803. [PubMed: 28461007]
22. Aggarwal M, Bozkurt B, Panjath G, et al. Lifestyle modifications for preventing and treating heart failure. *Journal of the American College of Cardiology*. 2018;72(19):2391–2405. [PubMed: 30384895]

23. The SRG. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *The New England journal of medicine*. 2015;373(22):2103–2116. [PubMed: 26551272]
24. Ather S, Chan W, Chillar A, et al. Association of systolic blood pressure with mortality in patients with heart failure with reduced ejection fraction: a complex relationship. *American heart journal*. 2011;161(3):567–573. [PubMed: 21392613]
25. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Jama*. 2002;288(23):2981–2997. [PubMed: 12479763]
26. Proia KK, Thota AB, Njie GJ, et al. Team-based care and improved blood pressure control: a community guide systematic review. *American journal of preventive medicine*. 2014;47(1):86–99. [PubMed: 24933494]
27. Kiselev AR, Gridnev VI, Shvartz VA, Posnenkova OM, Dovgalevsky PY. Active ambulatory care management supported by short message services and mobile phone technology in patients with arterial hypertension. *Journal of the American Society of Hypertension : JASH*. 2012;6(5):346–355. [PubMed: 22995803]
28. Patel S, Jacobus-Kantor L, Marshall L, et al. Mobilizing your medications: an automated medication reminder application for mobile phones and hypertension medication adherence in a high-risk urban population. *J Diabetes Sci Technol*. 2013;7(3):630–639. [PubMed: 23759395]
29. Varleta P, Acevedo M, Akel C, et al. Mobile phone text messaging improves antihypertensive drug adherence in the community. *The Journal of Clinical Hypertension*. 2017;19(12):1276–1284. [PubMed: 28941056]
30. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129(8):837–847. [PubMed: 24345399]
31. Lane DA, Skjth F, Lip GY, Larsen TB, Kotecha D. Temporal trends in incidence, prevalence, and mortality of atrial fibrillation in primary care. *Journal of the American Heart Association*. 2017;6(5):e005155. [PubMed: 28455344]
32. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110(9):1042–1046. [PubMed: 15313941]
33. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J*. 2013;34(35):2746–2751. [PubMed: 23900699]
34. Morillo CA, Banerjee A, Perel P, Wood D, Jouven X. Atrial fibrillation: the current epidemic. *Journal of geriatric cardiology : JGC*. 2017;14(3):195–203. [PubMed: 28592963]
35. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. *Thrombosis and haemostasis*. 2013;110(08):213–222. [PubMed: 23595785]
36. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *The Lancet*. 2015;386(9989):154–162.
37. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial Fibrillation Begets Heart Failure and Vice Versa: Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction. *Circulation*. 2016;133(5):484–492. [PubMed: 26746177]
38. Batul SA, Gopinathannair R. Atrial Fibrillation in Heart Failure: a Therapeutic Challenge of Our Times. *Korean Circ J*. 2017;47(5):644–662. [PubMed: 28955382]
39. Ling LH, Kistler PM, Kalman JM, Schilling RJ, Hunter RJ. Comorbidity of atrial fibrillation and heart failure. *Nat Rev Cardiol*. 2016;13(3):131–147. [PubMed: 26658575]
40. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107(23):2920–2925. [PubMed: 12771006]
41. Patel RB, Vaduganathan M, Rikhi A, et al. History of Atrial Fibrillation and Trajectory of Decongestion in Acute Heart Failure. *JACC Heart Fail*. 2019;7(1):47–55. [PubMed: 30409707]
42. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358(25):2667–2677. [PubMed: 18565859]

43. Moller M, Torp-Pedersen CT, Kober L. Dofetilide in patients with congestive heart failure and left ventricular dysfunction: safety aspects and effect on atrial fibrillation. The Danish Investigators of Arrhythmia and Mortality on Dofetilide (DIAMOND) Study Group. *Congestive heart failure* (Greenwich, Conn). 2001;7(3):146–150.
44. Ganesan AN, Nandal S, Luker J, et al. Catheter ablation of atrial fibrillation in patients with concomitant left ventricular impairment: a systematic review of efficacy and effect on ejection fraction. *Heart, lung & circulation*. 2015;24(3):270–280.
45. Hunter RJ, Berriman TJ, Diab I, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circulation Arrhythmia and electrophysiology*. 2014;7(1):31–38. [PubMed: 24382410]
46. Jones DG, Haldar SK, Hussain W, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *Journal of the American College of Cardiology*. 2013;61(18):1894–1903. [PubMed: 23500267]
47. Verma A, Kalman JM, Callans DJ. Treatment of patients with atrial fibrillation and heart failure with reduced ejection fraction. *Circulation*. 2017;135(16):1547–1563. [PubMed: 28416525]
48. Prabhu S, Taylor AJ, Costello BT, et al. Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction. The CAMERA-MRI Study. 2017;70(16):1949–1961.
49. Di Biase L, Mohanty P, Mohanty S, et al. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. *Circulation*. 2016;133(17):1637–1644. [PubMed: 27029350]
50. Marrouche NF, Brachmann J, Andresen D, et al. Catheter Ablation for Atrial Fibrillation with Heart Failure. *New England Journal of Medicine*. 2018;378(5):417–427. [PubMed: 29385358]
51. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125–e151. [PubMed: 30686041]
52. Goyal P, Almarzooq ZI, Cheung J, et al. Atrial fibrillation and heart failure with preserved ejection fraction: Insights on a unique clinical phenotype from a nationally-representative United States cohort. *International journal of cardiology*. 2018;266:112–118. [PubMed: 29887426]
53. Zafir B, Lund LH, Laroche C, et al. Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J*. 2018;39(48):4277–4284. [PubMed: 30325423]
54. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *Jama*. 2013;310(19):2050–2060. [PubMed: 24240932]
55. Lam CSP, Rienstra M, Tay WT, et al. Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction. Association With Exercise Capacity, Left Ventricular Filling Pressures, Natriuretic Peptides, and Left Atrial Volume. 2017;5(2):92–98.
56. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *Journal of the American College of Cardiology*. 2014;64(21):2222–2231. [PubMed: 25456757]
57. Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation: Vicious Twins. *Journal of the American College of Cardiology*. 2016;68(20):2217–2228. [PubMed: 27855811]
58. Cha YM, Wokhlu A, Asirvatham SJ, et al. Success of ablation for atrial fibrillation in isolated left ventricular diastolic dysfunction: a comparison to systolic dysfunction and normal ventricular function. *Circulation Arrhythmia and electrophysiology*. 2011;4(5):724–732. [PubMed: 21747059]
59. Kelly JP, DeVore AD, Wu J, et al. Rhythm Control Versus Rate Control in Patients With Atrial Fibrillation and Heart Failure With Preserved Ejection Fraction: Insights From Get With The Guidelines-Heart Failure. *J Am Heart Assoc*. 2019;8(24):e011560. [PubMed: 31818219]

60. Sobue Y, Watanabe E, Lip GYH, et al. Thromboembolisms in atrial fibrillation and heart failure patients with a preserved ejection fraction (HFpEF) compared to those with a reduced ejection fraction (HFrEF). *Heart and vessels*. 2018;33(4):403–412. [PubMed: 29067492]
61. Xiong Q, Lau YC, Senoo K, Lane DA, Hong K, Lip GY. Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials. *Eur J Heart Fail*. 2015;17(11):1192–1200. [PubMed: 26335355]
62. Savarese G, Giugliano RP, Rosano GM, et al. Efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation and heart failure: a meta-analysis. *JACC: Heart Failure*. 2016;4(11):870–880. [PubMed: 27614940]
63. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *Jama*. 2019;321(13):1261–1274. [PubMed: 30874766]
64. Khan MN, Jaïs P, Cummings J, et al. Pulmonary-Vein Isolation for Atrial Fibrillation in Patients with Heart Failure. *New England Journal of Medicine*. 2008;359(17):1778–1785. [PubMed: 18946063]
65. Roglic G WHO Global report on diabetes: A summary. *International Journal of Noncommunicable Diseases*. 2016;1(1):3.
66. Control CfD, Prevention. National diabetes statistics report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services. 2017.
67. Rowley WR, Bezold C, Arian Y, Byrne E, Krohe S. Diabetes 2030: Insights from Yesterday, Today, and Future Trends. *Popul Health Manag*. 2017;20(1):6–12. [PubMed: 27124621]
68. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes care*. 2004;27(8):1879–1884. [PubMed: 15277411]
69. Dei Cas A, Fonarow GC, Gheorghiade M, Butler J. Concomitant Diabetes Mellitus and Heart Failure. *Current problems in cardiology*. 2015;40(1):7–43. [PubMed: 25499908]
70. Dunlay SM, Givertz MM, Aguilar D, et al. Type 2 Diabetes Mellitus and Heart Failure, A Scientific Statement From the American Heart Association and Heart Failure Society of America. *Journal of cardiac failure*. 2019;25(8):584–619. [PubMed: 31174952]
71. Sandesara PB, O'Neal WT, Kelli HM, et al. The Prognostic Significance of Diabetes and Microvascular Complications in Patients With Heart Failure With Preserved Ejection Fraction. *Diabetes Care*. 2018;41(1):150–155. [PubMed: 29051160]
72. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *Jama*. 1979;241(19):2035–2038. [PubMed: 430798]
73. Marwick TH, Ritchie R, Shaw JE, Kaye D. Implications of underlying mechanisms for the recognition and management of diabetic cardiomyopathy. *Journal of the American College of Cardiology*. 2018;71(3):339–351. [PubMed: 29348027]
74. Dauriz M, Targher G, Laroche C, et al. Association Between Diabetes and 1-Year Adverse Clinical Outcomes in a Multinational Cohort of Ambulatory Patients With Chronic Heart Failure: Results From the ESC-HFA Heart Failure Long-Term Registry. *Diabetes Care*. 2017;40(5):671–678. [PubMed: 28255009]
75. From AM, Leibson CL, Bursi F, et al. Diabetes in heart failure: prevalence and impact on outcome in the population. *The American journal of medicine*. 2006;119(7):591–599. [PubMed: 16828631]
76. Allen LA, Magid DJ, Gurwitz JH, et al. Risk factors for adverse outcomes by left ventricular ejection fraction in a contemporary heart failure population. *Circulation: Heart Failure*. 2013;6(4):635–646. [PubMed: 23709659]
77. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995–2008. [PubMed: 31535829]
78. Das SR, Everett BM, Birtcher KK, et al. 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *Journal of the American College of Cardiology*. 2018;72(24):3200–3223. [PubMed: 30497881]

79. Association AD. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2019. *Diabetes Care*. 2019;42(Supplement 1):S103–S123. [PubMed: 30559236]
80. Castagno D, Baird-Gunning J, Jhund PS, et al. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. *Am Heart J*. 2011;162(5):938–948.e932. [PubMed: 22093212]
81. Elder DH, Singh JS, Levin D, et al. Mean HbA1c and mortality in diabetic individuals with heart failure: a population cohort study. *Eur J Heart Fail*. 2016;18(1):94–102. [PubMed: 26663216]
82. Aguilar D, Bozkurt B, Ramasubbu K, Deswal A. Relationship of hemoglobin A1C and mortality in heart failure patients with diabetes. *Journal of the American College of Cardiology*. 2009;54(5):422–428. [PubMed: 19628117]
83. Vaduganathan M, Patel RB, Singh A, et al. Prescription of Glucagon-Like Peptide-1 Receptor Agonists by Cardiologists. *Journal of the American College of Cardiology*. 2019;73(12):1596–1598. [PubMed: 30922481]
84. Vaduganathan M, Sathiyakumar V, Singh A, et al. Prescriber Patterns of SGLT2i After Expansions of U.S. Food and Drug Administration Labeling. *Journal of the American College of Cardiology*. 2018;72(25):3370–3372. [PubMed: 30409566]
85. Patel RB, Al Rifai M, McEvoy JW, Vaduganathan M. Implications of Specialist Density for Diabetes Care in the United States. *JAMA cardiology*. 2019.
86. Gunawan F, Partridge C, Kosiborod M, Inzucchi S. SUN-149 Cardiologist vs. Endocrinologist Encounters in Patients with T2D and CVD: Potential Implications for Glucose-Lowering Therapy Use and Education. *J Endocr Soc*. 2019;3(Suppl 1):SUN-149.
87. Davis BR, Piller LB, Cutler JA, et al. Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Circulation*. 2006;113(18):2201–2210. [PubMed: 16651474]
88. Bozkurt B, Aguilar D, Deswal A, et al. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. *Circulation*. 2016;134(23):e535–e578. [PubMed: 27799274]
89. Berl T, Hunsicker LG, Lewis JB, et al. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Annals of internal medicine*. 2003;138(7):542–549. [PubMed: 12667024]
90. Kasai T, Bradley TD. Obstructive sleep apnea and heart failure: pathophysiologic and therapeutic implications. *Journal of the American College of Cardiology*. 2011;57(2):119–127. [PubMed: 21211682]
91. Komajda M, Anker SD, Cowie MR, et al. Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: data from the QUALIFY global survey. *Eur J Heart Fail*. 2016;18(5):514–522. [PubMed: 27095461]
92. Peri-Okonny PA, Mi X, Khariton Y, et al. Target Doses of Heart Failure Medical Therapy and Blood Pressure: Insights From the CHAMP-HF Registry. *JACC Heart Fail*. 2019;7(4):350–358. [PubMed: 30738978]
93. Malha L, Mann SJ. Loop Diuretics in the Treatment of Hypertension. *Current hypertension reports*. 2016;18(4):27. [PubMed: 26951244]
94. Colucci WS, Kolia TJ, Adams KF, et al. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction: the REversal of VEntricular Remodeling with Toprol-XL (REVERT) trial. *Circulation*. 2007;116(1):49–56. [PubMed: 17576868]
95. Exner DV, Dries DL, Waclawiw MA, Shelton B, Domanski MJ. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the studies of left ventricular dysfunction. *Journal of the American College of Cardiology*. 1999;33(4):916–923. [PubMed: 10091816]
96. Investigators* S. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *New England Journal of Medicine*. 1992;327(10):685–691. [PubMed: 1463530]

97. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *The Lancet*. 2003;361(9372):1843–1848.
98. Ekeruo IA, Solhpour A, Taegtmeier H. Metformin in Diabetic Patients with Heart Failure: Safe and Effective? *Curr Cardiovasc Risk Rep*. 2013;7(6):417–422. [PubMed: 24466358]
99. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *Jama*. 2019;322(12):1155–1166.
100. Group NS, Holman RR, Haffner SM, et al. Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med*. 2010;362(16):1463–1476. [PubMed: 20228402]
101. Holman RR, Coleman RL, Chan JCN, et al. Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2017;5(11):877–886. [PubMed: 28917545]
102. Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia. *New England Journal of Medicine*. 2012;367(4):319–328. [PubMed: 22686416]
103. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAZone Clinical Trial In macroVascular Events): a randomised controlled trial. *The Lancet*. 2005;366(9493):1279–1289.
104. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *The Lancet*. 2009;373(9681):2125–2135.
105. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *New England Journal of Medicine*. 2015;373(23):2247–2257. [PubMed: 26630143]
106. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2016;375(4):311–322. [PubMed: 27295427]
107. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2016;375(19):1834–1844. [PubMed: 27633186]
108. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2017;377(13):1228–1239. [PubMed: 28910237]
109. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392(10157):1519–1529. [PubMed: 30291013]
110. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. *New England Journal of Medicine*. 2013;369(14):1317–1326. [PubMed: 23992601]
111. White WB, Cannon CP, Heller SR, et al. Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. *New England Journal of Medicine*. 2013;369(14):1327–1335. [PubMed: 23992602]
112. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet*. 2015;385(9982):2067–2076. [PubMed: 25765696]
113. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2015;373(3):232–242. [PubMed: 26052984]
114. Fitchett D, Butler J, van de Borne P, et al. Effects of empagliflozin on risk for cardiovascular death and heart failure hospitalization across the spectrum of heart failure risk in the EMPA-REG OUTCOME® trial. *European heart journal*. 2017;39(5):363–370.
115. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine*. 2017;377(7):644–657. [PubMed: 28605608]
116. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019;380(4):347–357. [PubMed: 30415602]

Synopsis

Heart failure (HF) is a growing global epidemic and an increasingly cumbersome burden on healthcare systems worldwide. As such, optimal management of existing comorbidities in the setting of HF is particularly important to prevent disease progression, reduce HF hospitalizations, and improve quality of life. Given the increasing complexity of HF, adequate management of concomitant comorbidities is reliant upon 1) processes ensuring prescription and delivery of guideline-directed therapies, 2) collaboration between subspecialist physicians and all providers to provide comprehensive care, and 3) shared decision making with patients to determine optimal, individual strategies for comorbidity management. In this review, we address 3 key comorbidities commonly associated with HF: hypertension, atrial fibrillation, and diabetes mellitus. We comprehensively describe the epidemiology, management, and emerging therapies in these 3 disease states as they relate to the overall HF syndrome.

Key Points:

- Hypertension, atrial fibrillation (AF), and diabetes are comorbidities that alter the trajectory of HF and require specialized management.
- Aggressive treatment of hypertension is beneficial in patients with Stage A and Stage B HF. In Stage C HF, hypertension management occurs in parallel with maximization of guideline-directed therapies.
- The management of AF in HF is complex and requires comprehensive evaluation of 1) etiology of cardiomyopathy, 2) left ventricular function, 3) symptom burden, and 4) discussion regarding benefits and risks of procedural therapies for AF.
- Several novel glucose-lowering therapies have demonstrated particular benefit in the setting of HF. Sodium-glucose cotransporter 2 inhibitors represent a glucose-lowering therapy that has emerged as a cornerstone of therapy in HF with reduced ejection fraction, regardless of diabetes status.

Figure 1: Hypertension Management in Established Heart Failure

ACE-I= angiotensin converting enzyme inhibitors; ARB= angiotensin receptor blocker; ARNI= angiotensin receptor-neprilysin inhibitor; BP= blood pressure; CCBs= calcium channel blocker; GDMT= guideline directed medical therapy; HF = heart failure; HFpEF= heart failure with preserved ejection fraction; HFrEF= heart failure with reduced ejection fraction; MRA= mineralocorticoid receptor antagonist; OSA = obstructive sleep apnea

Atrial Fibrillation Management in Chronic Heart Failure

① Comprehensive, Personalized Assessment of AF

- Ensure accurate documentation of AF
- Assess AF burden and rate control
- Evaluation of patient symptoms and correlation with AF
- Consideration of patient-specific pathology (LVEF, nature of cardiomyopathy, cardiac and non-cardiac comorbidities)
- Understanding of patient preference and values
- **Lifestyle counseling:** encourage weight loss, ensure strict control of HTN and DM, and screen for OSA

② Choose Initial Rate or Rhythm Control Strategy

Factors favoring **Rate Control**

- Failure of rhythm control
- Patient preference
- Limited correlation between AF and HF symptoms and hospitalizations

Factors favoring **Rhythm Control**

- Failure of rate control
- Repeat HF hospitalizations with AF as trigger
- Symptomatic AF
- Patient preference

Treatment Options

- β blockers 1st line in HFrEF
- Avoidance of non-dihydropyridine CCBs in HFrEF
- Frequent reassessment of efficacy of rate control strategy (may require monitoring)
- Consider AV nodal ablation with PPM or CRT-P in refractory cases

Treatment Options

- Consider CA as first line in select HFrEF patients to reduce hospitalizations/mortality
- After DCCV or CA, consider maintenance AAD including dofetilide, amiodarone, or sotalol
- Avoidance of dronedarone in HFrEF and Class IC agents in all HF
- CA in symptomatic HF patients after failed AAD

③ Anticoagulation unless contraindications

Figure 2: Atrial Fibrillation Management in Chronic Heart Failure

AAD= anti-arrhythmic drug; AF= atrial fibrillation; AV = atrioventricular; CA= catheter ablation; CCBs= calcium channel blocker; CRT-P= cardiac resynchronization therapy pacemaker; DCCV = direct current cardioversion; DM= diabetes mellitus; HF = heart failure; HFpEF= heart failure with preserved ejection fraction; HFrEF= heart failure with reduced ejection fraction; HTN= hypertension; LVEF= left ventricular ejection fraction; OSA= obstructive sleep apnea; PPM = permanent pacemaker

Figure 3: Diabetes Management in Chronic Heart Failure

CV = cardiovascular; DKA= diabetic ketoacidosis; GFR= glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA_{1c} = hemoglobin A_{1c}; HF = heart failure; HFpEF= heart failure with preserved ejection fraction; HFrEF= heart failure with reduced ejection fraction; PCP= primary care physician; SGLT2= sodium glucose transporter 2

Table 1:**Management of Hypertension By ACC/AHA Stage of Heart Failure**

Stage A HF	Stage B HF	Stage C HF
<ul style="list-style-type: none"> • Heart healthy lifestyle • Aggressive BP Management <ul style="list-style-type: none"> – Target BP <130/80 to reduce risk of overt HF¹⁴ • Choosing Specific Agent <ul style="list-style-type: none"> – Chlorthalidone is associated with reduced HF risk compared with amlodipine or lisinopril⁸⁷ – Calcium-channel blockers, thiazide diuretics, ACE-I or ARB are appropriate first line agents⁸⁸ – In diabetic patients with nephropathy, ARB have been shown to efficacious in reducing incident HF risk⁸⁹ • Secondary HTN work-up in patients with persistent HTN <ul style="list-style-type: none"> – Including OSA screening⁹⁰ 	<ul style="list-style-type: none"> • In patients with LV dysfunction, there is robust data supporting the use of ACE-I and β blockers in promoting LV recovery⁹⁴⁻⁹⁷ • While these LV benefits are not exclusive to a HTN population, many patients with LV dysfunction also have HTN • Avoidance of non-dihydropyridine calcium channel blockers and alpha-adrenergic blockers²⁵ 	<ul style="list-style-type: none"> • Heart healthy lifestyle • Systolic BP goal <130 mmHg • <u>Heart Failure with Reduced Ejection Fraction</u> <ul style="list-style-type: none"> – Optimization of β blocker, ACE-I/ARB or ARNI, and MRA to target levels – ARNI in particular has potent anti-hypertensive effects²⁵ – Vast majority of patients are not appropriately uptitrated to target doses despite significant room in their BP^{91,92} • <u>Heart Failure with Preserved Ejection Fraction</u> <ul style="list-style-type: none"> – Consider MRA to reduce HF hospitalization – Consider ARNI in select subgroups (i.e., women, mid-range EF) • Diuretics <ul style="list-style-type: none"> – Loop diuretics have minimal anti-hypertensive effects compared to thiazide diuretics⁹³ – Thiazide diuretics can be considered in patients with minimal congestive symptoms and persistently high BP • Secondary HTN work up in patients with persistent HTN, including OSA screening⁹⁰

ACC/AHA: American College of Cardiology/American Heart Association; ACE-I: angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BP = blood pressure; HF = heart failure; HTN = hypertension; LV = left ventricular; MRA = mineralocorticoid receptor antagonist; OSA = obstructive sleep apnea

Table 2.
Impact of Glucose-Lowering Therapies on Heart Failure Outcomes: A Summary of Randomized Clinical Trials.

	Mechanism	Key RCTs		HF Specific Data	Disadvantages
Metformin	Decreases hepatic glucose production; Decreases intestinal absorption of glucose; Increases insulin sensitivity	None		Safe in HF patients ⁹⁸	Nausea, abdominal discomfort
Sulfonylureas	Closure of ATP-sensitive potassium channels to stimulate insulin release from β -cells	CAROLINA: non-inferiority trial of linagliptin vs glimepiride in DM patients with elevated CV risk ⁹⁹		No difference in HF hospitalization with glimepiride compared with linagliptin ⁹⁹	Hypoglycemia, weight gain
Meglitinides	Closure of ATP-sensitive potassium channels to stimulate insulin release from β -cells	NAVIGATOR: 9,306 participants with impaired fasting glucose randomized to nateglinide or placebo ¹⁰⁰		No difference in HF hospitalization with nateglinide: HR= 0.85 (95% CI: 0.64–1.14)	
α -glucosidase Inhibitors	Delay carbohydrate digestion; reduces rate of intestinal glucose absorption	ACE: 6,522 patients with impaired glucose tolerance and CAD randomized to acarbose or placebo ¹⁰¹		No difference in HF hospitalization: HR = 0.89 (95% CI: 0.63–1.24)	
Insulin	Several mechanisms leading to direct and indirect uptake of glucose in cells	ORIGIN: randomized 12,537 patients with DM or pre-DM with CV risk factors to standard of care or insulin glargine ¹⁰²		No difference in HF hospitalization with insulin glargine compared to standard of care: HR= 0.90, (95% CI: 0.77–1.05) ¹⁰²	Cost; Hypoglycemia
Thiazolidinediones	Activating PPAR nuclear receptors leads to upregulation of genes resulting in decreased insulin resistance	PROACTIVE: 5238 patients with DM and macrovascular disease randomized to pioglitazone or placebo ¹⁰³		Increased risk of HF admission ¹⁰³	Edema, reduction of bone mineral density, increased HF hospitalizations
		RECORD: 4447 patients with DM on metformin or sulfonylurea monotherapy randomized to addition of rosiglitazone or combination of metformin or sulfonylurea ¹⁰⁴		Increased risk of HF causing hospitalization or death with rosiglitazone: HR= 2.1 (95% CI: 1.35– 3.27) ¹⁰⁴	
GLP-1 Receptor Agonists	Stimulates GLP-1 receptors thereby increasing insulin secretion and improving insulin sensitivity	Lixisenatide	ELIXA: 6068 patients with DM and ACS randomized to lixisenatide or placebo ¹⁰⁵	No difference in HF hospitalization: HR= 0.96, (95% CI: 0.75 to 1.23) ¹⁰⁵	GI upset, headache
		Liraglutide	LEADER: 9340 patients with DM, high CV risk to receive liraglutide or placebo ¹⁰⁶	No difference in HF hospitalization: HR = 0.87, (95% CI: 0.73–1.05) ¹⁰⁶	
		Semaglutide	SUSTAIN-6: 3297 patients with DM randomized to semaglutide or placebo ¹⁰⁷	No difference in HF hospitalization: HR= 1.11, (95% CI: 0.77 to 1.61) p= 0.57 ¹⁰⁷	
			PIONEER 6: 3182 patients randomized to oral semaglutide vs. placebo in DM (non-inferiority trial)	No difference in HF hospitalization: HR=0.86 (95% CI: 0.48–1.55)	
			SOUL: Oral semaglutide vs. placebo in DM (superiority trial)	Trial Ongoing	

	Mechanism	Key RCTs		HF Specific Data	Disadvantages
DPP-4 Inhibitors	Slows the inactivation and degradation of GLP-1	Exenatide	EXSCCEL: 14,752 patients with DM +/- CAD were randomized to exenatide or placebo ¹⁰⁸	No difference in HF hospitalization: HR = 0.94, (95% CI: 0.78–1.13) ¹⁰⁸	GI problems, flu-like symptoms
		Albiglutide	HARMONY OUTCOMES: 9,463 patients with DM and CVD randomized to albiglutide or placebo ¹⁰⁹	No difference in composite of CV death or HF hospitalization: HR = 0.85 (95% CI: 0.70–1.04)	
		Dulaglutide	REWIND: 9,901 patients with DM randomized to dulaglutide or placebo	No difference in HF hospitalization: HR = 0.93 (95% CI: 0.77–1.12)	
		Saxagliptin	SAVOR-TIMI-53: 16,492 patients with DM with history or at high risk of CVD were randomized to saxagliptin or placebo ¹¹⁰	Increased rate of HF hospitalization: HR = 1.27, (95% CI: 1.07 to 1.51) ¹¹⁰	
		Alogliptin	EXAMINE: 5380 patients with DM and ACS within 90 days to alogliptin or placebo ¹¹¹	No difference in HF hospitalization: HR = 1.07, (95% CI: 0.79–1.46) ¹¹²	
		Sitagliptin	TECOS: 14,671 patients with DM and established CVD were assigned to sitagliptin or placebo ¹¹³	No differences in rates of hospitalization for HF: HR = 1.00, (95% CI: 0.83 to 1.20) ¹¹³	
		Linagliptin	CAROLINA: non-inferiority trial of linagliptin vs glimepiride in DM patients with elevated CV risk ⁹⁹	No difference in HF hospitalization with linagliptin compared with glimepiride	
SGLT-2 Inhibitors	Inhibits SGLT-2 in proximal-convoluted tubule to prevent reabsorption of glucose and sodium	Empagliflozin	EMPA-REG OUTCOME: 7,020 patients with established CVD randomized to empagliflozin or placebo ¹¹⁴	Reduction in HF hospitalization: HR = 0.65, (95% CI: 0.50–0.85) ¹¹⁴	Genital yeast infections, urinary tract infections, increased urination, dehydration, constipation
			EMPEROR-REDUCED: empagliflozin or placebo in HF+EF	<i>Trial ongoing</i>	
			EMPEROR-PRESERVED: empagliflozin or placebo in HFpEF	<i>Trial ongoing</i>	
			EMPULSE HF: empagliflozin vs. placebo in acute hospitalized HF	<i>Trial ongoing</i>	
		Canagliflozin	CANVAS: 10,142 patients with DM and high CV risk assigned to canagliflozin or placebo ¹¹⁵	Reduction in HF hospitalization: HR = 0.67 (95% CI: 0.52 to 0.87) ¹¹⁵	
			CHIEF-HF: 1,900 patients with HF randomized to canagliflozin or placebo	<i>Trial ongoing</i>	
		Dapagliflozin	DECLARE-TIMI 58: 17,160 patients with DM with or at risk for CVD randomized to dapagliflozin or placebo ¹¹⁶	Reduction in HF hospitalization: HR = 0.73 (0.61–0.88) ¹¹⁶	

	Mechanism	Key RCTs		HF Specific Data	Disadvantages
				Reduction in CV mortality or worsening HF regardless of DM status: HR=0.74 (95% CI: 0.65–0.85)	
			DELIVER: dapagliflozin vs placebo in HFpEF	<i>Trial ongoing</i>	
		Sotagliflozin *	SOLOIST-WHF-sotagliflozin vs placebo in HFrEF after admission for worsening HF	<i>Trial ongoing</i>	
		Ertugliflozin	VERTIS CV: ertugliflozin vs, placebo in DM with CVD	<i>Trial ongoing</i>	

* combined SGLT-1/SGLT-2 inhibitor

ACS = acute coronary syndrome; ATP = adenosine triphosphate; CAD = coronary artery disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; GI = gastrointestinal; GLP-1 RA = glucagon-like peptide-1; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; SGLT2= sodium glucose transporter 2