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JACC STATE-OF-THE-ART REVIEW

Implications of Atrial Fibrillation for Guideline-Directed Therapy in Patients With Heart Failure

JACC State-of-the-Art Review

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ABSTRACT

Atrial fibrillation (AF) and heart failure (HF) are common cardiovascular conditions that frequently coexist. Among patients with HF, more than one-half also have AF. Both are associated with significant morbidity and mortality. Moreover, the prevalence of each is increasing globally, and this trend is expected to continue owing to an aging population and increased life expectancy. Diagnosis of AF in a patient with HF is associated with greater symptom burden, more frequent hospitalizations, and a worse prognosis. Guideline-directed medical therapy (GDMT) for HF can affect the incidence of AF. Once present, AF can influence the efficacy of some components of GDMT for HF. In this review, we discuss the effect of GDMT for HF across the spectrum of ejection fraction on prevention of AF as well as the benefit of GDMT in patients with vs without AF. (J Am Coll Cardiol 2024;83:932-950) © 2024 by the American College of Cardiology Foundation.

EPIDEMIOLOGY AND PROGNOSIS OF ATRIAL FIBRILLATION AND HEART FAILURE

The prevalence of atrial fibrillation (AF) is increasing worldwide due to increased life expectancy and improved survival from other cardiovascular conditions.[1,2] In the United States, the prevalence of AF is forecast to increase to 12.1 million by 2030, a rapid rise from around 5.2 million in 2010.[1,3] Similar trends are present in Europe, where the prevalence of AF among patients >55 years is expected to increase to 17.9 million by 2060 from 8.8 million in 2010.[1,2] AF accounts for up to 30% of all ischemic strokes and is associated with depression, vascular dementia, impaired quality of life, and increased mortality.[4]

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HIGHLIGHTS

- AF and HF commonly occur concurrently, and the combination is associated with worse prognosis than either condition alone.
- GDMT for HF can reduce the incidence of AF.
- Further research is needed to clarify the benefit of GDMT for HF in patients with concomitant AF across the range of left ventricular ejection fractions.

Similarly, heart failure (HF) prevalence in the United States and Europe is expected to rise by 2030, again owing to the advancing age of the population.[1,4] Although implementation of guideline-directed medical therapy (GDMT) is associated with a 25% reduction in all-cause death at 24 months in heart failure with reduced ejection fraction (HFrEF), morbidity and mortality remain high.[5] Furthermore, initiation of GDMT is often delayed and many patients do not receive target doses.[6]

Owing to mutual risk factors and interaction between the 2 conditions, AF and HF coexist in up to 50% of patients.[1] In an analysis of Framingham Heart Study participants that developed new-onset AF or HF, 32% of patients diagnosed with HF had a previous history of AF and an additional 30% were diagnosed with AF thereafter. Among patients with new-onset AF, 8% had a previous diagnosis of HF and an additional 28% were later diagnosed with HF.[7] A diagnosis of AF among patients with HF has been associated with worse outcomes (**Table 1**).[8,9]

RISK FACTORS FOR AF IN HF

Risk factors for AF such as advancing age, coronary and peripheral artery disease, smoking, physical inactivity, obesity, chronic kidney disease, hypertension, obstructive and central sleep apnea, metabolic syndrome, and diabetes are prevalent among patients with HF.[10,11] Among modifiable risk factors, hypertension accounts for the greatest population-attributable risk for both AF and HF.[12,13] Owing to commonality among risk factors as well as the pathophysiology of HF discussed below, HF is a risk factor for incident AF and is associated with a higher risk of stroke in AF.[11]

Among patients with HF, AF appears to be most prevalent in heart failure with preserved ejection fraction (HFpEF). In an analysis of the Swedish HF Registry, AF prevalence increased sequentially among patients with HFrEF (ejection fraction [EF] <40%), heart failure with midrange ejection fraction (HFmrEF; EF 40%-49%), and HFpEF (EF ≥50%) from 53% to 60% to 65%, respectively.[14] AF was also more prevalent in patients with HFpEF than in those with HFrEF in the Framingham Heart Study (62% vs 55%; $P = 0.02$).[7]

PATHOPHYSIOLOGY OF AF IN PATIENTS WITH HF

HF can lead to the development of AF through multiple mechanisms (**Central Illustration**). Chronically elevated left atrial pressures result in atrial fibrosis and scarring, which culminates in slowed conduction velocity and shortened action potential duration and effective refractory period, both of which promote re-entry and AF perpetuation.[11,15] Furthermore, the pulmonary veins are an important site in the pathophysiology of AF,[16] and chronically elevated left atrial pressure has been shown to lead to alterations in pulmonary vein myocyte firing, which promotes AF development and propagation.[17] AF may also result in mitral and tricuspid regurgitation owing to annular enlargement leading to elevated filling pressures and resultant fibrosis.[18,19]

Angiotensin II induces adverse atrial remodeling through activation of profibrotic pathways, including those mediated by aldosterone. The release of proinflammatory cytokines, including transforming growth factor (TGF)-β1, leads to changes in the electrical properties of the atrial myocytes and predisposes to the development of AF.[20,21]

Atrial myocytes of patients with HF have decreased expression of atrial L-type calcium channels, which results in reduced calcium entry into the cell with myocyte depolarization and thus less calcium-induced calcium release from the sarcoplasmic reticulum. This culminates in an increased frequency of delayed after-depolarizations and susceptibility to arrhythmias.[17]

PATHOPHYSIOLOGY OF HF IN PATIENTS WITH AF

HF can result directly from AF in the form of tachycardia-induced cardiomyopathy, a diagnosis in which left ventricular dysfunction caused by AF with rapid ventricular rate corrects with resolution of the tachyarrhythmia. The pathophysiology of tachycardia-induced cardiomyopathy is complex and involves electrical remodeling and abnormalities in

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
ARB = angiotensin receptor blocker
BB = beta-blocker
EF = ejection fraction
GDMT = guideline-directed medical therapy
HF = heart failure
HFmrEF = heart failure with midrange ejection fraction
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
MRA = mineralocorticoid receptor antagonist
RAAS = renin-angiotensin-aldosterone system
SGLT2 = sodium-glucose cotransporter-2

TABLE 1 Atrial Fibrillation and Prognosis in Heart Failure

First Author	Population	Outcome	HR for Comparison[a]				*P* for Interaction
			Overall	HFrEF	HFmrEF	HFpEF	
Olsson et al[29]	CHARM trials	All-cause mortality	-	LVEF ≤40% HR: 1.38 (95% CI: 1.21-1.59)	-	LVEF >40% HR: 1.80 (95% CI: 1.46-2.21)	0.041
Maggioni et al[48]	Val-HeFT	All-cause mortality	-	LVEF <40% HR: 1.40 (95% CI: 1.10-1.78); *P* = 0.005	-	-	-
Linssen et al[31]	COACH trial	HF hospitalization or all-cause mortality	-	LVEF <40% HR: 1.05 (95% CI: 0.80-1.38); *P* = 0.72	-	LVEF ≥40% HR: 1.49 (95% CI: 1.04-2.14); *P* = 0.03	-
Eapen et al[28]	Medicare claims data	All-cause mortality	HR: 1.08 (95% CI: 1.03-1.14); *P* = 0.003	LVEF <40% HR: 1.00 (95% CI: 0.94-1.08); *P* = 0.92	-	LVEF ≥40% HR: 1.16 (95% CI: 1.08-1.25); *P* < 0.001	<0.001
Sartipy et al[14]	Swedish Heart Failure Registry	All-cause mortality	-	LVEF <40% HR: 1.17 (95% CI: 1.11-1.23)	LVEF 40%-49% HR: 1.22 (95% CI: 1.12-1.33)	LVEF ≥50% HR: 1.11 (95% CI: 1.02-1.21)	-
Zafrir et al[27]	European Society of Cardiology HF long-term registry	All-cause mortality or HF hospitalization	-	LVEF <40% HR: 0.957 (95% CI: 0.843-1.087); *P* = 0.502	LVEF 40%-49% HR: 1.302 (95% CI: 1.055-1.608); *P* = 0.014	LVEF ≥50% HR: 1.365 (95% CI: 1.152-1.619); *P* < 0.001	-

[a]Comparator for HRs in all studies was sinus rhythm.

CHARM = Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity; COACH = Comparison of Outcomes and Access to Care for Heart Failure; HFmrEF = heart failure with midrange ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; Val-HeFT = Valsartan Heart Failure Trial.

calcium homeostasis with downstream sequelae resulting in left ventricular systolic dysfunction.[22] AF is one of the most common causes of tachycardia-induced cardiomyopathy.[11]

AF causes HF through multiple other mechanisms as well. In AF, left ventricular filling is impaired by a loss of effective atrial contractility and shortened diastolic filling times owing to an increased resting heart rate and an irregular ventricular rhythm.[23] Together, these result in a reduction in cardiac output and an elevation in intracardiac pressures. Left atrial dilation from AF can result in atrial functional mitral regurgitation. Significant secondary mitral regurgitation is associated with a high symptom burden and poor quality of life.[24,25]

Importantly, AF-induced left atrial dilation and atrial and ventricular fibrosis can lead directly to HFpEF.[26] This may explain the increased prevalence of AF among patients with HFpEF compared with HFrEF.[7,14]

PROGNOSTIC IMPLICATIONS OF AF IN HF

Among patients with HF, the presence of a secondary diagnosis of AF is associated with greater symptom burden and hospitalizations across the spectrum of EF (Table 1).[27] AF has also been associated with increased mortality, although there may be heterogeneity based on EF. While some studies suggest that AF portends a worse prognosis only among patients with HFpEF and HFmrEF, others have identified increased mortality risk across the EF spectrum.[9,14,27-31] An analysis of >12,000 patients enrolled in ENGAGE-AF TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) found that among patients with AF, those with HFrEF had a higher rate of hospitalizations for HF and mortality than those with HFpEF.[30]

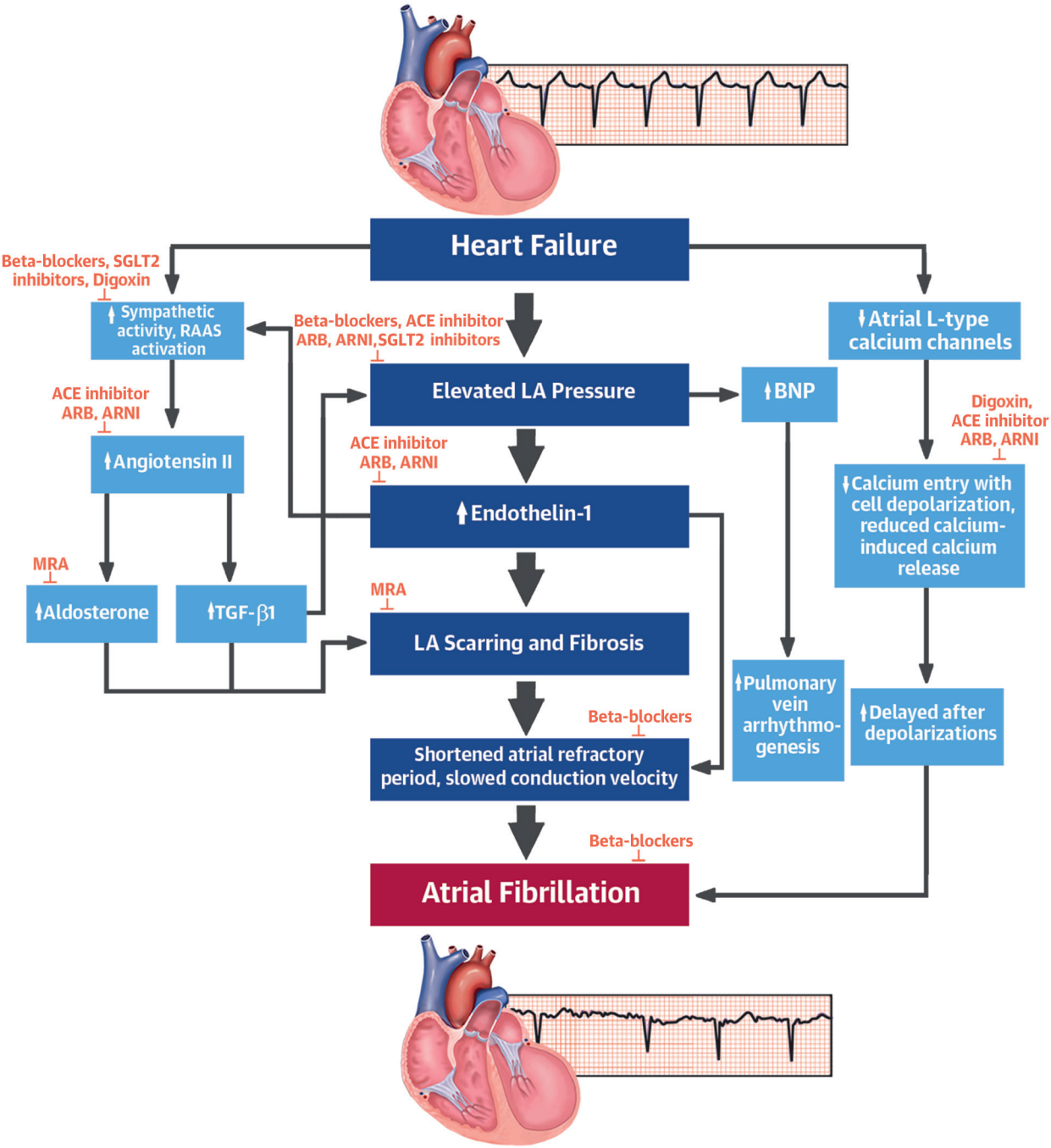
AF burden also has prognostic significance among those with HF. In an analysis of >25,000 patients with HF, increasing AF burden was associated with an increased risk of HF hospitalization and mortality.[32] Similarly, patients with HF and subclinical AF lasting <24 hours who progressed to having clinical AF or subclinical AF lasting >24 hours had a higher rate of HF hospitalization (8.9% per year) than those without progression (2.5% per year).[33]

PREVENTION OF AF WITH GDMT AND IMPACT OF AF ON EFFICACY OF GDMT

AF has important implications for GDMT in HF (Table 2). Components of GDMT can prevent the development of AF in patients being treated for HF. Once AF develops, it appears to influence the efficacy of some GDMT (Table 3).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS. HF is characterized by excess sympathetic activity and activation of the renin-angiotensin-aldosterone system (RAAS). With activation of the RAAS, angiotensin II binds its receptor and leads to increased systemic vascular resistance, aldosterone release from the adrenal cortex, sympathetic nerve release of noradrenalin, and myocyte fibrosis.[34]

CENTRAL ILLUSTRATION **Mechanisms of Atrial Fibrillation in Heart Failure**



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HF leads to AF via multiple intertwined pathways. HF activates the renin-angiotensin-aldosterone system (RAAS) and increases sympathetic activity. This results in increased levels of angiotensin II and release of aldosterone and transforming growth factor (TGF)-β1. Aldosterone and TGF-β1 promote left atrial scarring and fibrosis indirectly, via increases in left atrial pressure and release of endothelin-1, as well as directly. The resultant shortening of the atrial refractory period and slowed conduction velocity caused by left atrial scarring promotes AF. Elevated left atrial pressure also stimulates release of B-type natriuretic peptide (BNP) which increases pulmonary vein arrhythmogenesis and AF. Finally, atrial L-type calcium channels are decreased in HF, leading to less calcium entry with cell depolarization and calcium-induced calcium release. This increases the frequency of delayed after-depolarizations and promotes AF. Guideline-directed medical therapy for HF can counter these pathologic mechanisms at various points. ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; HF = heart failure; MRA = mineralocorticoid receptor agonist; SGLT2 = sodium-glucose cotransporter-2.

TABLE 2 Studies Evaluating the Implications of Atrial Fibrillation for Guideline-Directed Medical Therapy in Heart Failure

First Author	Population	LVEF Inclusion Criteria	Study Drug	Outcome	Numbers in Study	Result
[a]Vermes et al[45]	SOLVD trial from a single center without AF on baseline ECG	≤35%	Enalapril	Incidence of AF	n = 374 (n = 186 enalapril; n = 188 placebo)	10 (5.4%) in enalapril group vs 45 (24%) in placebo group ($P < 0.0001$); HR: 0.22 (95% CI: 0.11-0.44); $P < 0.0001$
[a]Alsheikh-Ali et al[47]	SOLVD trial	≤35%	Enalapril	Hospitalization for atrial tachyarrhythmia	n = 6,797 (n = 3,396 enalapril; n = 3,401 placebo)	7.9 hospitalizations per 1,000 patient-years of follow-up in enalapril group vs 12.4 per 1,000 patient-years in the placebo group; RR: 0.64 (95% CI: 0.48-0.85); $P = 0.002$
[a]Maggioni et al[48]	Val-HeFT without AF on baseline ECG	<40%	Valsartan	Incidence of AF	n = 4,395 (n = 2,205 valsartan; n = 2,190 placebo)	113 (5.12%) in valsartan group vs 174 (7.95%) in placebo group; $P = 0.0002$; HR: 0.63 (95% CI: 0.49-0.81); $P = 0.0003$.
[b]Ducharme et al[49]	CHARM Program without AF on baseline ECG	CHARM-Alternative and CHARM-Added: ≤40%; CHARM-Preserved: >40%	Candesartan	Incidence of new AF	n = 6,379 (n = 3,191 candesartan; n = 3,188 placebo)	Overall: 177 (5.55%) in the candesartan group vs 215 (6.74%) in the placebo group; OR: 0.812 (95% CI: 0.662-0.998) $P = 0.048$. CHARM-Added and CHARM-Alternative: OR: 0.779 (95% CI: 0.608-0.997); $P = 0.047$. CHARM-Preserved: OR: 0.894 (95% CI: 0.618-1.295). P value for heterogeneity between trials: 0.57.
[b]Liu et al[55]	PARAMOUNT, PARADIGM-HF, EVALUATE-HF, PARAGON-HF, PIONEER-HF, and OUTSTEP-HF	No LVEF criteria	Sacubitril/valsartan (comparator arm: enalapril or valsartan)	Incidence of AF	n = 15,512 (n = 7,750 sacubitril/valsartan; n = 7,762 control)	694 (9.0%) in sacubitril/valsartan group vs 650 (8.4%) in the control group; RR: 1.07 (95% CI: 0.95-1.19); $P = 0.26$.
[c]Cikes et al[56]	PARAGON-HF	≥45%	Sacubitril/valsartan	Incidence of new AF	n = 2,219 without previous AF	Intention-to-treat analysis: HR: 1.06 (95% CI: 0.83-1.35); $P = 0.64$. On-treatment analysis: HR: 1.05 (95% CI: 0.81-1.37); $P = 0.70$.
[a]McMurray et al[70]	CAPRICORN	≤40% (3-21 days after myocardial infarction)	Carvedilol	Incidence of AF and atrial flutter	Overall: n = 1,959 (n = 975 carvedilol; n = 984 placebo); Excluding preexisting AF: n = 1,789 (n = 894 carvedilol; n = 895 placebo)	Overall: 22 (2.3%) in the carvedilol group vs 53 (5.4%) in the placebo group; HR: 0.41 (95% CI: 0.25-0.68); $P = 0.0003$. Excluding patients with preexisting AF: 16 (1.8%) carvedilol group vs 31 (3.5%) placebo group; HR: 0.51 (95% CI: 0.28-0.93); $P = 0.025$.
[a]Rienstra et al[71]	COPERNICUS, MERIT-HF, CIBIS-II, and SENIORS	<35%	Various beta-blockers	All-cause mortality	Overall: n = 8,680 (n = 4,482 BB; n = 4,198 placebo); AF and HF group: n = 1,677 (n = 842 BB; n = 835 placebo); SR and HF group: n = 7,003 (n = 3,640 BB; n = 3,363 placebo)	Overall: 416 events in BB group, 750 events in placebo group; OR: 0.68 (95% CI: 0.59-0.77); $P < 0.01$. AF and HF group: 114 events in BB group, 131 events in placebo group; OR: 0.86 (95% CI: 0.66-1.13); $P = 0.28$. SR and HF group: 302 events in BB group, 439 events in placebo group OR: 0.63 (95% CI: 0.54-0.73); $P < 0.01$.

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TABLE 2 Continued

First Author	Population	LVEF Inclusion Criteria	Study Drug	Outcome	Numbers in Study	Result
[c]Kotecha et al[72]	10 randomized HF trials	Predominantly (though not entirely) <50%	Various beta-blockers	All-cause mortality	n = 17,009	AF group: HR: 0.97 (95% CI: 0.83-1.14); $P = 0.73$. SR group: HR: 0.73 (95% CI: 0.67-0.80); $P < 0.001$.
[b]Nielsen et al[73]	Three nationwide registries	No LVEF criteria	Various beta-blockers	All-cause mortality	Unmatched cohort: n = 39,741 (n = 19,464 BB; 20,277 non-BB); Propensity-matched cohort: n = 23,896 (n = 11,948 BB; n = 11,948 non-BB)	Unmatched cohort: 1-year mortality rate per 100 person-years: 37.2 in BB group vs 23.2 in non-BB group. Propensity-matched cohort: 1-year mortality rate per 100 person-years: 17.8 in BB group vs 10.8 in non-BB group; HR: 0.75 (95% CI: 0.71-0.79).
[a]Cadrin-Tourigny et al[74]	AF-CHF	≤35% with AF	Various beta-blockers	All-cause mortality	Propensity-matched cohort: n = 655 (n = 426 BB; n = 229 non-BB)	95 (42%) in the non-BB group vs 136 (31%) in the BB group; HR: 0.72 (95% CI: 0.549-0.945); $P = 0.018$.
[a]Swedberg et al[88]	EMPHASIS-HF	≤35%	Eplerenone	Incidence of new-onset AF; Effect of AF on study drug efficacy	n = 1,794 (n = 911 eplerenone, n = 883 placebo)	New-onset AF: 25 (2.7%) in eplerenone group vs 40 (4.5%) in placebo group; HR: 0.58 (95% CI: 0.35-0.96); $P = 0.034$. Death from cardiovascular causes or hospitalization for HF: No AF at baseline: HR: 0.70 (95% CI: 0.57-0.85); AF at baseline: HR: 0.60 (95% CI: 0.46-0.79); P for interaction = 0.41.
[c]Neefs et al[89]	TOPCAT	≥45% without permanent AF	Spironolactone	Risk of new-onset AF or recurrence of AF	No previous history of AF: n = 2,228 (n = 1,111 spironolactone; n = 1,117 placebo); Previous AF: n = 505 (n = 260 spironolactone; n = 245 placebo)	Incidence of new-onset AF: 58 (5.2%) in spironolactone group vs 49 (4.4%) in placebo group; $P = 0.41$; HR: 1.19 (95% CI: 0.81-1.74); $P = 0.38$. AF recurrence: 30 (11.5%) in spironolactone group vs 29 (11.8%) in placebo group; $P = 1.00$. HR: 0.94 (95% CI: 0.57-1.58); $P = 0.83$.
[c]Cikes et al[90]	TOPCAT (North and South American patients)	≥45%	Spironolactone	Incidence of new-onset AF; CV mortality, aborted cardiac arrest, and HF hospitalization	No previous history of AF: n = 1,005 (n = 503 spironolactone; n = 502 placebo); History of AF alone: n = 314 (n = 169 spironolactone; n = 145 placebo); AF at enrollment: n = 446 (n = 214 spironolactone; n = 232 placebo)	Incidence of new-onset AF: HR: 0.98, (95% CI: 0.68-1.42); $P = 0.92$. No AF: HR: 0.79 (95% CI: 0.62-1.00); $P = 0.047$. History of AF alone: HR: 1.06 (95% CI: 0.70-1.59); $P = 0.80$. AF at enrollment: HR: 0.80 (95% CI: 0.58-1.10) $P = 0.17$; P for interaction = 0.49.

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Angiotensin-converting enzyme (ACE) inhibition and angiotensin receptor blockade have been shown to reduce morbidity and mortality in patients with HFrEF[35-39] and are recommended for patients with HF who are unable to take an angiotensin receptor-neprilysin inhibitor.[4,40]

There are multiple mechanisms by which angiotensin II mediates AF. First, binding of angiotensin II to its receptor results in production of TGF-β1, which promotes cardiac fibroblast proliferation.[41] Experimental animal models suggest that the atria are more susceptible to TGF-β1-induced fibrosis than the ventricles.[42] Second, the increase in systemic vascular resistance, sympathetic activity, and myocardial fibrosis induced by angiotensin II results in elevations in left atrial pressures. Elevations in left atrial pressures affect the atrial myocyte action potential, including a shortening of atrial refractory periods,

TABLE 2 Continued

First Author	Population	LVEF Inclusion Criteria	Study Drug	Outcome	Numbers in Study	Result
[a]Butt et al[9]	DAPA-HF	≤40%	Dapagliflozin	Incidence of new-onset AF; Effect of AF on study drug efficacy	No previous history of AF: n = 2,834 (n = 1,419 dapagliflozin; n = 1,415 placebo); History of AF: n = 1,910 (n = 954 dapagliflozin; n = 956 placebo)	Incidence of new-onset AF: 66 (4.7%) in placebo group and 57 (4.0%) in dapagliflozin group; HR: 0.86 (95% CI: 0.60-1.22). Worsening HF or cardiovascular death (events per 100 person-years): No AF at baseline: 10.8 in dapagliflozin group vs 14.7 placebo group; HR: 0.74 (95% CI: 0.62-0.88); AF at baseline: 12.7 in dapagliflozin group vs 16.9 in placebo group; HR: 0.75 (95% CI: 0.62-0.92). *P* for interaction = 0.88.
[c]Filippatos et al[102]	EMPEROR-PRESERVED	≥40%	Empagliflozin	Incidence of new-onset AF; Effect of AF on study drug efficacy	No previous history of AF: n = 2,853 (n = 1,417 empagliflozin; n = 1,427 placebo); History of AF: n = 3,135 (n = 1,576 empagliflozin; n = 1,559 placebo)	Incidence of new-onset AF: 116 (8.0%) in empagliflozin group vs 119 (8.1%) in placebo group; HR: 1.00 (95% CI: 0.77-1.29); *P* = 0.98. First HF hospitalization or CV death (events per 100 patient-years): No AF: 5.91 in empagliflozin group vs in 7.74 placebo group; HR: 0.78 (95% CI: 0.64-0.95); AF: 7.72 in empagliflozin group vs 9.57 in placebo group; HR: 0.78 (95% CI: 0.66-0.93); *P* for interaction = 0.96.
[c]Butt et al[103]	DELIVER	≥40%	Dapagliflozin	Effect of AF on study drug efficacy	No previous history of AF: n = 2,709 (n = 1,372 dapagliflozin; n = 1,337 placebo); History of AF: n = 3,552 (n = 1,758 dapagliflozin; n = 1,794 placebo)	CV death or worsening HF (events per 100 person-years): No AF: 7.2 in empagliflozin group vs 8.1 in placebo group; HR: 0.89 (95% CI: 0.74-1.08); Any AF: 8.3 in empagliflozin group vs 10.8 in placebo group; HR: 0.78 (95% CI: 0.67-0.90); *P* for interaction = 0.426.
[b]Whitbeck et al[108]	AFFIRM	No LVEF restriction, analysis limited to enrolled patients with HF	Digoxin	All-cause mortality	n = 1,076	HR: 1.41 (95% CI: 1.09-1.84); *P* = 0.010.
[b]Gheorghiade et al[105]	AFFIRM	No LVEF restriction	Digoxin	All-cause mortality	Propensity-matched cohort: n = 1,756 (n = 878 digoxin [n = 140 HF]; n = 878 nondigoxin [n = 147 HF])	Propensity-matched analysis (not limited to HF patients): 124 (14%) in digoxin group vs 118 (13%) in nondigoxin group; HR: 1.06 (95% CI: 0.83-1.37); *P* = 0.64. Subgroup analysis of matched cohort limited to HF patients: 38 (27%) in digoxin group vs 39 (27%) in nondigoxin group; HR: 1.08 (95% CI: 0.69-1.69); *P* = 0.74.
[a]Swedberg et al[111]	SHIFT	≤35%	Ivabradine	Incidence of AF (safety outcome)	n = 6,558 (n = 3,268 ivabradine; n = 3,200 placebo)	306 (9%) ivabradine vs 251 (8%) placebo; *P* = 0.012.

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TABLE 2 Continued

First Author	Population	LVEF Inclusion Criteria	Study Drug	Outcome	Numbers in Study	Result
[c]Komajda et al[116]	EDIFY	≥45%	Ivabradine	Incidence of AF (safety outcome)	n = 179 (n = 95 ivabradine; n = 84 placebo)	7 (7.4%) ivabradine vs 6 (7.1%) placebo; *P* = nonsignificant.
[a]Ponikowski et al[8]	VICTORIA	<45%	Vericiguat	Incidence of new-onset AF; Effect of AF on study drug efficacy	No AF: n = 2,661; History of AF alone: n = 992; AF on ECG at enrollment: n = 1,357; Any AF: n = 2,349	Incidence of new-onset AF (events per 100 person-years): 7.5 in vericiguat group vs 8.7 in placebo group; HR: 0.93 (95% CI: 0.75-1.15); *P* = 0.51. CV death or HF hospitalization (events per 100 person-years): No AF: 31.2 in vericiguat group vs 36.2 in placebo group; HR: 0.84 (95% CI: 0.74-0.96); *P* = 0.001; History of AF: 36.6 in vericiguat group vs 40.6 in placebo group; HR: 0.90 (95% 0.74-1.11); *P* = 0.33; AF on ECG at enrollment: 36.7 in vericiguat group vs 37.8 in placebo group; HR: 0.97 (95% CI: 0.81-1.16); *P* = 0.77; Any AF: 36.6 in vericiguat group vs 39.0 in placebo group; HR: 0.94 (95% CI: 0.83-1.08); *P* = 0.40. *P* for interaction = 0.45.
[a]Solomon et al[123]	GALACTIC-HF	≤35%	Omecamtiv mecarbil	Time to first HF event or CV death	No AF: n = 5,987 (n = 2,974 omecamtiv mecarbil; n = 3,013 placebo); AF: n = 2,245 (n = 1,146 omecamtiv mecarbil; n = 1,099 placebo)	No AF: 981 (33%) in omecamtiv mecarbil group vs 1,103 (36%) in placebo group; HR: 0.87 (95% CI: 0.80-0.95); AF: 542 (47%) in omecamtiv mecarbil group vs 504 (46%) in placebo group; HR: 1.05 (95% CI: 0.93-1.18); *P* for interaction = 0.012. No AF, no digoxin: 854 (32%) omecamtiv mecarbil vs 948 (35%) placebo; HR: 0.88 (95% CI: 0.81-0.97); AF, no digoxin: 370 (45%) omecamtiv mecarbil vs 365 (48%) placebo; HR: 0.94 (95% CI: 0.81-1.09); No AF, digoxin: 127 (36%) omecamtiv mecarbil vs 155 (44%) placebo; HR: 0.74 (95% CI: 0.58-0.93); AF, digoxin: 172 (50%) omecamtiv mecarbil vs 139 (40%) placebo; HR: 1.34 (95% CI: 1.07-1.69); *P* for interaction = 0.007.
[b]Packer et al[130]	CABANA	No LVEF criteria, analysis limited to enrolled patients with HF	Ablation	Death, disabling stroke, serious bleeding, or cardiac arrest	n = 778 (n = 378 ablation; n = 400 medical therapy)	Primary composite endpoint: 34 (9%) in ablation group vs 49 (12.3%) in drug therapy group; HR: 0.64 (95% CI: 0.41-0.99). Death from any cause: 23 (6.1%) in ablation group vs 37 (9.3%) in drug therapy group; HR: 0.57 (95% CI: 0.33-0.96).

Continued on the next page

TABLE 2 Continued

First Author	Population	LVEF Inclusion Criteria	Study Drug	Outcome	Numbers in Study	Result
[a]Marrouche et al[131]	CASTLE-AF	≤35%	Ablation	Death from any cause of HF hospitalization	n = 363 (n = 179 ablation; n = 184 medical therapy)	Primary endpoint: 51 (28.5%) in ablation group vs 82 (44.6%) in medical therapy group; HR: 0.62 (95% CI: 0.43-0.87); $P = 0.007$. All-cause mortality: 24 (13.4%) in ablation group vs 46 (25.0%) in medical therapy group; HR: 0.53 (95% CI: 0.32-0.86); $P = 0.01$.
[a]Sohns et al[132]	CASTLE-HTx	Advanced HF referred for transplant evaluation	Ablation	Death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation	n = 194 (n = 97 ablation group; n = 97 medical therapy)	Primary endpoint: 8 (8%) in ablation group vs 29 (30%) in medical therapy group; HR: 0.24 (95% CI: 0.11-0.52); $P < 0.001$. Death from any cause: 6 (6%) in ablation group vs 19 (20%) in medical therapy group; HR: 0.29 (95% CI: 0.12-0.72).
[b]Rillig et al[135]	EAST-AFNET 4	No LVEF criteria (56% HFpEF, 27% HFmrEF, 17% HFrEF)	Rhythm control	Composite of CV death, stroke, or hospitalization for HF or acute coronary syndrome	n = 798 (n = 396 early rhythm control group; n = 402 usual care)	Primary endpoint: 94 (23.7%) in early rhythm control group vs 130 (32.3%) in usual care; HR: 0.74 (95% CI: 0.56-0.97); $P = 0.03$.
[c]Chieng et al[134]	AF Ablation for HFpEF: A Randomized Controlled Trial	≥50%	Ablation	Difference in peak pulmonary capillary wedge pressure (PCWP) on exercise right heart catheterization (RHC) from baseline to 6 mo	n = 31 (n = 16 ablation group; n = 15 medical therapy group)	Ablation group: peak PCWP on baseline exercise RHC 30.4 ± 4.2 mm Hg vs 25.4 ± 4.5 mm Hg at 6 mo; $P < 0.01$. Medical therapy group: peak PCWP on baseline exercise RHC 29.5 ± 3.9 mm Hg vs 28.9 ± 5.3 mm Hg at 6 mo; $P = 0.68$.

[a]HFrEF. [b]Variable LVEF. [c]HFmrEF/HFpEF.

AF-CHF = Atrial Fibrillation and Congestive Heart Failure; AFFIRM = AF Follow-Up Investigation of Rhythm Management; BB = beta-blocker; CABANA = Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation; CAPRICORN = Carvedilol Post-Infarct Survival Control in LV Dysfunction; CASTLE-AF = Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; CASTLE-HTx = Catheter Ablation for Atrial Fibrillation in Patients with End-Stage Heart Failure and Eligibility for Heart Transplantation; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; CV = cardiovascular; DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER = Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EAST-AFNET 4 = Early Treatment of Atrial Fibrillation for Stroke Prevention Trial; ECG = electrocardiogram; EDIFY = Preserved left ventricular ejection fraction chronic heart failure with ivabradine study; EMPEROR-Preserved = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EVALUATE-HF = Effects of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients with Heart Failure with Reduced Ejection Fraction; GALACTIC-HF = Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure; HFmrEF = heart failure with midrange ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; OUTSTEP-HF = Randomized Study Using Accelerometry to Compare Sacubitril/Valsartan and Enalapril in Patients with Heart Failure; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; PARAGON-HF = Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction; PARAMOUNT = Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction; PIONEER-HF = Comparison of Sacubitril/Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode; SENIORS = Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure; SHIFT = Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial; SOLVD = Studies of Left Ventricular Dysfunction; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; VICTORIA = Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction.

which increases susceptibility to AF.[41,43] Finally, angiotensin II may directly affect atrial myocyte electrophysiology.[41]

While ACE inhibitors are of unclear benefit in preventing AF among patients with hypertension,[44] secondary analyses of HF trials provide evidence that ACE inhibitors prevent new-onset AF. In an analysis of 374 patients without a previous history of AF enrolled in the SOLVD (Studies of Left Ventricular Dysfunction) trial from a single center, patients randomized to enalapril were less likely to develop new onset AF.[45] Similarly, a study investigating trandolapril among patients with left ventricular systolic dysfunction following myocardial infarction found that among patients in sinus rhythm at the time of study entry, randomization to the trandolapril group was associated with a reduction in incident AF.[46] In a separate analysis of the SOLVD trial, ACE inhibitors reduced clinically significant AF that resulted in hospitalizations and mortality.[47]

Similar findings have been reported for patients with HFrEF receiving angiotensin receptor blockers (ARBs). Among 4,395 patients in sinus rhythm at the time of enrollment into Val-HeFT (Valsartan Heart

TABLE 3 Therapies With Mortality Benefit in HF and Interactions With AF

	HFrEF			HFmrEF and HFpEF		
	Decrease AF Incidence	Decrease Mortality in SR	Decrease Mortality in AF	Decrease AF Incidence	Decrease Mortality in SR	Decrease Mortality in AF
ACEI	✓	✓	NR/U	NR/U	X	X
ARB	✓	✓	✓	✓	X	X
ARNI	X (compared with ACEI or ARB)	✓	✓	X (compared with ACEI or ARB)	✓[a]	X
BB	✓	✓	NR/U	NR/U	✓[a]	NR/U
MRA	✓	✓	✓	X	✓[a]	✓
SGLT2i	X	✓	✓	X	✓	✓
Rhythm control	✓	N/A	✓	✓	N/A	✓
Ablation	✓	N/A	✓	✓	N/A	Ongoing clinical trial

[a]Benefit may exist primarily in the lower range of preserved EF spectrum.

✓ = data exist supporting use of the drug class for achieving the specified endpoint; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BB = beta-blocker; HFmrEF = heart failure with midrange ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; N/A = not applicable; NR/U = not reported/uncertain, ie, insufficient evidence to determine whether the drug class achieves the specified endpoint; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SR = sinus rhythm; X = no data exist supporting use of the drug class for achieving the specified endpoint.

Failure Trial), 5.12% in the valsartan arm developed AF compared with 7.95% of patients assigned to placebo (HR: 0.63; 95% CI: 0.49-0.81; $P = 0.0003$).[48] In a composite analysis of the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity) trials, patients assigned to candesartan were less likely to develop AF during follow-up across the spectrum of EF.[49]

The comparative effectiveness of ACE inhibitors on morbidity and mortality among patients with vs without AF has not been reported in post hoc analyses of large randomized controlled trials. However, an analysis of the CHARM Program found that candesartan reduced cardiovascular death or hospitalization due to HF regardless of the presence or absence of AF at the time of enrollment.[29]

ANGIOTENSIN-NEPRILYSIN INHIBITORS. Sacubitril/valsartan is a combination of an ARB and a neprilysin inhibitor. Neprilysin in an endopeptidase that is involved in degradation of bradykinin, natriuretic peptides, angiotensin II, and adrenomedullin, some of which counter the deleterious consequences of sympathetic overactivation characteristic of HF.[50] Sacubitril/valsartan has been shown to be superior to ACE inhibitors in decreasing morbidity and mortality among patients with HFrEF.[50] Sacubitril/valsartan also has benefit among patients with HFpEF and HFmrEF, particularly among those patients with an EF on the lower end of this spectrum.[51]

Calcium mishandling is a key contributor to the development of AF.[52] Nonhuman animal models have shown that sacubitril/valsartan enhances function of the ryanodine receptors and thus can decrease calcium mishandling.[53] Sacubitril/valsartan may also provide benefits for patients already in AF. In one study, mice underwent rapid atrial pacing to simulate AF and were randomized to either sacubitril/valsartan for 3 weeks or control. Mice that received sacubitril/valsartan had less atrial and ventricular remodeling and fibrosis, longer atrial refractory periods, and lower levels of collagen and N-terminal pro-B-type natriuretic peptide (NT-proBNP).[54]

In a meta-analysis of 6 studies of patients with HF (regardless of EF), sacubitril/valsartan did not result in a lower incidence of AF compared with either enalapril or valsartan.[55] Similarly, an analysis of PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) found that randomization to sacubitril/valsartan did not result in a lower incidence of AF among those without a previous history of AF at the time of enrollment.[56] However, smaller studies suggest that there may be benefit to sacubitril/valsartan in promoting reverse atrial remodeling among patients with AF. In a study which randomized 64 patients to receive either 160 mg/d valsartan or 200 mg/d sacubitril/valsartan after catheter ablation for AF, patients that received sacubitril/valsartan had a decrease in atrial size, findings which were not present in the valsartan group.[57] Similarly, in a retrospective study of patients with AF being treated with either sacubitril/valsartan or valsartan alone who underwent transesophageal and transthoracic echocardiography on the same day, patients treated with sacubitril/valsartan had higher left atrial peak systolic strain, left atrial appendage emptying velocity, and left atrial appendage EF and a lower incidence of spontaneous echo contrast. In a mouse model, investigators replicated these findings and demonstrated a reduction in fibrotic area size among mice treated with sacubitril/valsartan.[58]

The morbidity and mortality benefits of sacubitril/valsartan among patients with HFrEF were not attenuated by the presence of AF in PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure).[51] Similarly, the treatment effects of sacubitril/valsartan were not affected by AF in a secondary analysis of PARAGON-HF.[56]

BETA-BLOCKERS. Certain beta-blockers (BBs) decrease mortality, hospitalizations, and symptom burden in HFrEF and are associated with an improvement in EF.[59-61] Thus, carvedilol, metoprolol succinate, and bisoprolol are recommended for all patients with HFrEF unless contraindicated.[4,40] These benefits likely extend to patients with HFmrEF.[62] Notably, evidence from studies enrolling patients with HFpEF both with and without AF suggest that BBs may worsen symptoms in the HFpEF cohort.[63,64] Among patients with AF, BBs are commonly used for rate control and are recommended for use in patients with AF regardless of EF.[10,65]

Binding of ligand to the β-adrenergic receptor results in activation of adenyl cyclase and production of cyclic adenosine monophosphate (AMP) via a G-protein-mediated mechanism. Cyclic AMP activates protein kinase A, which leads to increased intracellular calcium and positive chronotropic and inotropic effects. HF is characterized by excess activation of the sympathetic nervous system and resultant downregulation of myocardial β-adrenergic receptors and uncoupling of the receptors from their G-protein-mediated effects. Chronic BB therapy results in increased β-adrenergic receptor signal density and restoration of receptor-G-protein coupling.[66]

BBs are first-line therapies for rate control in AF.[67] Beta-blockade exerts benefit via negative chronotropic effects which aid in rate control. BBs may also prevent AF via numerous proposed mechanisms. BBs prevent adverse remodeling and promote positive remodeling which can result in a reduction in left atrial pressure, a common trigger for AF. Similarly, excess sympathetic drive promotes atrial arrhythmias and is opposed by beta-blockade. Stimulation of the β-adrenergic receptors results in a shortening of action potential duration which is a potential trigger for the initiation and maintenance of AF, and experimental data suggest that BBs may reverse these changes.[68] Finally, BBs may prevent atrial ischemia and fibrosis.[69]

In the CAPRICORN (Carvedilol Post-Infarct Survival Control in LV Dysfunction) trial, patients randomized to carvedilol experienced a lower incidence of AF and atrial flutter.[70] An antiarrhythmic effect of BBs in HF was further supported in a meta-analysis of nearly 12,000 patients that demonstrated a reduction in incident AF from 39 to 28 events per 1,000 patient-years.[69] It remains uncertain whether BBs reduce incident AF in patients with HFmrEF and HFpEF.

Whether the mortality benefits of BBs in HFrEF are attenuated by the presence of AF remains uncertain. In a meta-analysis of patients enrolled in COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival), MERIT-HF (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II), and SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure), BBs did not reduce HF hospitalizations or mortality among patients with AF at the time of study entry, suggesting that the benefit of BBs is limited to those in sinus rhythm.[71] In a patient-level meta-analysis from the Beta-Blockers HF Collaborative Group that included >18,000 patients from 10 randomized trials, beta-blockade was associated with a significant reduction in mortality among patients with HFrEF in sinus rhythm (HR for all-cause mortality: 0.73; 95% CI: 0.67-0.80) but not among those in AF (HR: 0.97; 95% CI: 0.83-1.14; $P = 0.73$).[72]

Observational studies have challenged these findings. In a nationwide cohort study of patients with AF and HFrEF, HFmrEF, or HFpEF from Nielsen et al, BBs were associated with a reduction in all-cause mortality.[73] A secondary analysis of the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) study that propensity-matched patients who did not receive BBs to those who did found that patients treated with BBs had a significantly lower risk of all-cause mortality (HR: 0.72; 95% CI: 0.55-0.95) but not of hospitalizations (HR: 0.886; 95% CI: 0.72-1.10).[74]

The reason for these divergent results likely relates to the limitations of each study. In the trials included in each of the meta-analyses, patients were classified to AF vs sinus rhythm based on a single electrocardiogram at the time of enrollment. This raises the possibility that patients with paroxysmal AF may have been misclassified to the sinus rhythm group. Notably, the prevalence of AF was fewer than 20% at baseline in both meta-analyses despite registry studies suggesting AF is present in >50% of patients with HF.[14,71,73]

Each observational study also has important limitations. The study by Nielsen et al[73] included patients with HFrEF, HFmrEF, and HFpEF, but the investigators were unable to separate these patients into different categories. Importantly, BBs exert different degrees of benefit among patients with HFrEF, HFmrEF, and HFpEF, so this distinction is important.[59-61,63,64,75] Furthermore, the registry did not include data on NYHA functional classification or BB dose, both of which influence patient outcomes.

The study by Cadrin-Tourigny et al[74] was a secondary analysis of the AF-CHF trial, which randomized patients with HFrEF and AF to either rate or rhythm control. The investigators propensity-matched patients that received BB therapy to those that did not to determine whether BBs improved outcomes in AF and HFrEF. Before propensity matching, patients that received BBs were younger and more likely to have nonischemic cardiomyopathy, receive oral anticoagulation, and have an implantable cardioverter-defibrillator. Each of these factors has been associated with a better outcome, thus raising concern that residual confounding factors influenced the results even after propensity matching.[76]

Given ongoing uncertainty surrounding the benefits of BB in patients with AF and HF, a randomized trial examining this question may be warranted, although further data from large registries may help to clarify this issue.

MINERALOCORTICOID RECEPTOR ANTAGONISTS. In HF, RAAS activation results in excess aldosterone release with resultant binding to the mineralocorticoid receptor. This has numerous deleterious consequences including salt and water retention, increased blood pressure, and activation of proinflammatory and profibrotic pathways.[77,78] ACE inhibition results in transient reductions in aldosterone levels, although after 1 year, aldosterone is increased compared with baseline.[79] Among patients with HFrEF, mineralocorticoid receptor antagonists (MRAs) result in a reduction in HF hospitalizations and mortality.[80-82] MRAs did not reduce the primary composite outcome of death from cardiovascular outcomes, aborted cardiac arrest, or HF hospitalizations in the HFpEF trial TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist).[83] However, a subgroup analysis suggested there was benefit when evaluating only data from North and South America,[84] and a post hoc analysis suggested that patients with an EF on the lower end of normal may derive benefit.[85]

The incidence of AF is significantly increased among patients with hyperaldosteronism, which led to a hypothesis of aldosterone involvement in the pathogenesis of AF.[86] To further elucidate a potential mechanism, investigators implanted rats with osmotic minipumps that continuously delivered either aldosterone or a nonactive control. After 8 weeks, burst pacing resulted in AF in 11/11 rats that received aldosterone infusion compared with only 2/9 rats randomized to control ($P = 0.03$). In vivo right and left heart catheterization and ex vivo pressure-volume loop analysis in isolated working hearts did not demonstrate differences in ventricular function or atrial pressures between groups. In contrast, electrophysiologic mapping demonstrated prolongation of P-wave duration, total right atrial activation time, and local conduction times. Histologic examination revealed excess atrial fibroblasts and interstitial collagen in the aldosterone group, suggesting that aldosterone provides a substrate for AF via alterations in atrial conduction and fibrosis, without a significant impact from hemodynamic derangements.[87] Numerous animal studies have shown that MRAs decrease atrial fibrosis and AF.[78]

In a secondary analysis of EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), eplerenone significantly reduced the frequency of incident AF compared with placebo. Similarly, eplerenone reduced the composite endpoint of death from cardiovascular causes or hospitalization for HFrEF among patients with and without AF at the time of study enrollment.[88] In contrast, spironolactone did not reduce incident or recurrent AF in patients with HFpEF in a secondary analysis of TOPCAT.[89] A separate analysis of the same trial that included only patients randomized from North and South America also reported no difference in postrandomization incident AF between spironolactone and placebo. In that analysis, beneficial effects of spironolactone persisted regardless of AF status.[90] The IMPRESS-AF (Improved Exercise Tolerance in Heart Failure With Preserved Ejection Fraction by Spironolactone on Myocardial Fibrosis in Atrial Fibrillation) trial randomized 250 patients with HFpEF and AF to either spironolactone or placebo and found no difference in maximal oxygen consumption on cardiopulmonary exercise testing, 6-minute walk distance, or E/e′ ratio. Notably, there was a nonsignificant reduction in hospitalizations in the spironolactone group (15% vs 23%).[91]

Among patients with diabetes mellitus type 2 and chronic kidney disease, the MRA finerenone was shown to reduce both incident AF[92] and HF.[93] Whether finerenone has clinical benefits among patients with HFpEF is being explored in the ongoing FINEARTS-HF (Study to Evaluate the Efficacy [Effect on Disease] and Safety of Finerenone on Morbidity [Events Indicating Disease Worsening] & Mortality [Death Rate] in Participants With Heart Failure and Left Ventricular Ejection Fraction [Proportion of Blood Expelled Per Heart Stroke] Greater or Equal to 40%; NCT04435626).

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS. Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce HF hospitalizations and cardiovascular mortality among patients with HFrEF, HFmrEF, and HFpEF regardless of diabetic status.[94-98] The precise mechanism of benefit of SGLT2 inhibitors in HF is unknown but likely multimodal. The natriuretic

effects of SGLT2 inhibitors result in a reduction in intravascular volume and blood pressure. The resultant reduction in preload and afterload decreases reflex sympathetic hyperactivity. They also exert benefit by augmenting myocardial energy supply by increasing circulating ketones, which is a more effective myocardial energy source, and increasing levels of erythropoietin and thus hemoglobin, thereby improving myocardial oxygen supply. Furthermore, direct inhibition of the myocardial sodium-hydrogen exchanger improves mitochondrial function and reduces oxidative stress and arrhythmias. There is evidence that SGLT2 inhibitors decrease sympathetic and increase parasympathetic activity.[99] Increased thickness of epicardial adipose tissue has been associated with an increased incidence and severity of AF.[100] In a population of diabetic patients with coronary artery disease, dapagliflozin reduced epicardial adipose tissue volume.[101]

In a secondary analysis of the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58) trial, AF and atrial flutter events were significantly reduced among patients randomized to dapagliflozin, a finding which was consistent regardless of the presence or absence of HF at baseline.[100] In contrast, incident AF was not reduced among patients randomized to dapagliflozin in DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), although the benefits on dapagliflozin in terms of the primary outcome of death from cardiovascular causes or HF hospitalization, as well as all-cause mortality and quality-of-life endpoints, were consistent among patients with and without AF at baseline.[9] In EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction), empagliflozin did not reduce the frequency of incident AF among patients with HFpEF without a previous history of AF at the time of study enrollment, but the beneficial effects of the study drug in terms of the primary composite outcome of HF hospitalizations or cardiovascular death was present regardless of AF status.[102] Similar findings were evident in an analysis of the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) trial.[103]

DIGOXIN. Digoxin inhibits the sodium-potassium adenosine triphosphatase of myocardial cells, which promotes activity of the sodium-calcium exchanger, increased intracellular calcium, and increased force of myocardial contraction. Digoxin additionally has vagomimetic effects that slows sinoatrial and atrioventricular conduction.[104] Owing to a reduction in atrioventricular conduction from increased vagal tone, digoxin is useful for rate control in patients with AF.[105]

In the DIG (Digitalis Investigation Group) trial, patients with HF and EF ≤45% in sinus rhythm randomized to digoxin had fewer hospitalizations but no reduction in mortality.[106] Similar findings were noted in a subset of patients enrolled with HF and EF >45%.[106] Notably, a subsequent post hoc analysis suggested that there was mortality benefit among patients randomized to digoxin with serum digoxin concentration (SDC) 0.5-0.9 ng/mL.[107] Although AF was not a specified endpoint in the DIG trial, hospitalization for supraventricular arrhythmias was lower among patients randomized to digoxin.[106]

In one post hoc analysis of the AFFIRM (AF Follow-Up Investigation of Rhythm Management) trial that used propensity matching, there was an increased risk of all-cause, cardiovascular, and arrhythmic mortality among patients that received digoxin. This excess risk of all-cause mortality remained when limiting the analysis to only patients with HF.[108] Notably, that analysis was limited because patients in AFFIRM were randomized to rate or rhythm control, but not to a specific rate-controlling agent.[105] Furthermore, patients on digoxin in the AFFIRM trial were encouraged to aim for SDC ≥1 ng/mL, whereas the aforementioned post hoc analysis of the DIG trial suggested optimal dosing of digoxin at SDC 0.5-0.9 ng/mL.[105,107] A separate propensity-matched analysis of the same trial found no difference in mortality, hospitalization, or arrhythmic endpoints among patients taking digoxin.[105] In an analysis of the Swedish HF Registry, digoxin was associated with a reduction in HF hospitalizations and mortality among patients with HF and AF. Conversely, patients with HF but no history of AF receiving digoxin demonstrated an increased risk of HF hospitalization and mortality.[109]

Digoxin is frequently prescribed to patients with more advanced HF, and this may be difficult to account for even with propensity matching. There are 2 ongoing clinical trials evaluating the efficacy of digoxin among patients with HF while targeting lower SDCs. These trials are enrolling patients in sinus rhythm and AF (DIGIT-HF [Digoxin to Improve Outcomes in Patients with Advanced Chronic Heart Failure] [EudraCT 2013-005326-38], DECISION [Digoxin Evaluation in Chronic Heart Failure: Investigational Study In Outpatients in the Netherlands]; NCT03783429).[110]

IVABRADINE. Ivabradine is a selective inhibitor of the hyperpolarization-activated cyclic nucleotide-gated channels that produce the I_f current. Ivabradine does not have activity against other cardiac receptors or channels and thus imparts only negative

chronotropic effects.[111] It was previously thought that hyperpolarization-activated cyclic nucleotide-gated channels were present only in the sinoatrial node, but subsequent studies have demonstrated they are also expressed in other cardiac tissue, including the atrioventricular node.[112] In a small trial that randomized patients with uncontrolled permanent AF despite BB or calcium channel blocker therapy to the addition of ivabradine or digoxin, ivabradine decreased the mean daytime heart rate by 11.5% but was less effective than digoxin.[113]

In the SHIFT (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial), patients with HF and EF ≤35% on maximally tolerated BBs with a resting heart rate ≥70 beats/min were randomized to ivabradine or placebo. Patients with a history of persistent AF were excluded. Those that were randomized to ivabradine had a reduction in the composite outcome of hospital admission for worsening HF or cardiovascular death. Notably, patients who received ivabradine were more likely to develop AF or atrial flutter during the study period (9% in ivabradine group vs 8% in placebo group; $P = 0.01$).[111] A meta-analysis that included data from >40,000 patients found that ivabradine was associated with a >15% increased risk of AF.[114] Ivabradine affects I_f channels in the pulmonary veins, an important structural substrate for AF initiation and maintenance, thus providing a potential mechanism for this finding.[115] In the HFpEF trial EDIFY (Preserved left ventricular ejection fraction chronic heart failure with ivabradine study), which examined use of ivabradine for patients with EF ≥45%, AF incidence was not increased among patients assigned to the study drug, although the trial was relatively small (n = 179) and may have been underpowered for that endpoint.[116]

Although patients with AF were excluded from clinical trials evaluating ivabradine in HF populations because of a presumed lack of benefit, subsequent studies have revealed that ivabradine has heart rate-lowering effects in AF.[112,113,117] Whether benefits of ivabradine in terms of HF hospitalization and cardiovascular mortality are present among patients with preexisting persistent AF who otherwise fit the SHIFT enrollment criteria is unknown.

OTHER MEDICATIONS. The combination of hydralazine and nitrates for African-American patients with HFrEF resulted in a significant improvement in the composite endpoint of death from any cause, hospitalization for HF, and quality of life in the A-HeFT (African-American Heart Failure Trial).[118] This combination was found to have consistent benefits across a variety of subgroups, including those with AF the time of study enrollment.[119]

Vericiguat is an oral soluble guanylate cyclase stimulator. In the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial, patients with HF and EF ≤45% were randomized to either vericiguat or placebo on a background of GDMT. Patients that received vericiguat had a lower incidence of a composite outcome of death from cardiovascular causes and first hospitalization for HF.[120] A post hoc analysis revealed that treatment with vericiguat did not reduce the incidence of AF compared with placebo (7.5 vs 8.7 events/100 person-years; adjusted HR: 0.93; $P = 0.51$), however the beneficial effects of vericiguat on the primary composite outcome persisted regardless of baseline AF status.[8]

Omecamtiv mecarbil is a cardiac contractility modulator that acts by selectively binding to cardiac myosin and increasing the number of myosin heads available for interaction with actin. In GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure), omecamtiv mecarbil resulted in a lower incidence of a first HF event or cardiovascular death, but no significant difference in all-cause mortality or quality of life among patients with HFrEF.[121] In a prespecified analysis, the benefit of omecamtiv mecarbil was limited in those with AF at baseline.[122] When stratified for baseline digoxin use and AF, patients with AF who were taking digoxin and omecamtiv mecarbil had worse outcomes in terms of the primary composite outcome. In contrast, patients in sinus rhythm at study entry derived benefit from the study drug, including the subgroup taking digoxin.[123] Why omecamtiv mecarbil led to harm in patients with AF taking digoxin but not in patients in sinus rhythm taking digoxin is uncertain.[110,123] Of note, omecamtiv mecarbil was not approved for use by the U.S. Food and Drug Administration.

In the STEP-HFpEF (Subjects with Obesity-related HFpEF) trial, patients with HFpEF randomized to the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide had a greater improvement in quality of life and 6-minute walk distance compared with placebo. More than 50% of enrolled patients had AF at baseline. Notably, patients randomized to semaglutide had a lower rate of serious adverse events related to AF (1.1% vs 3.4%).[122] In contrast, liraglutide failed to improve clinical stability among patients with HFrEF and a recent HF hospitalization[124] and was associated with an increased risk of a serious cardiac events (10% vs 3%; $P = 0.04$) among stable outpatients with HFrEF.[125]

Studies have shown that GLP-1 receptor agonists are associated with an increase in heart rate.[126] Whether use of these agents may incite new AF is a

topic of uncertainty. In a meta-analysis of trials evaluating the cardiovascular safety of albiglutide, patients receiving the study drug had an increased risk of AF.[127] In contrast, a subsequent meta-analysis that included trials evaluating albiglutide and other GLP-1 agonists showed no increased risk of AF.[128]

RHYTHM CONTROL: A NEW FORM OF GDMT?

There is mounting evidence that rhythm control is associated with a decrease in morbidity and mortality among patients with AF,[129] and this benefit extends to those with concomitant HF. In a secondary analysis of the CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial,[130] patients with HF (79% HFpEF, 12% HFmrEF, 9% HFrEF) randomized to catheter ablation had a 36% relative reduction in the primary composite endpoint of death, disabling stroke, serious bleeding, or cardiac arrest, and a 43% relative risk reduction in all-cause mortality. These findings were similar to those in CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation), which demonstrated a 38% relative risk reduction in the composite outcome of death from cardiovascular causes and hospitalization for HF, and a 47% relative risk reduction in all-cause mortality among patients randomized to catheter ablation.[131] In CASTLE-HTx (Catheter Ablation for Atrial Fibrillation in Patients with End-Stage Heart Failure and Eligibility for Heart Transplantation), patients with advanced HF and symptomatic AF randomized to catheter ablation (compared with patients randomized to rhythm and/or rate control) had a significant reduction in the composite endpoint of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation (HR: 0.24; 95% CI: 0.11-0.52; $P < 0.001$).[132]

A prospective registry of patients with AF and EF ≥50% found that patients with HFpEF at the time of ablation experienced more AF recurrence, AF-related rehospitalization, and need for repeated AF ablation than those without HF. Furthermore, while patients without HFpEF who underwent AF ablation were found to have improvement in both physical component summary score and mental component summary score, no such improvement was noted for those with HFpEF.[133] In contrast, a small trial randomized 31 patients with HFpEF and AF to medical therapy alone or ablation. Compared with those in the medical therapy group, patients randomized to ablation demonstrated a reduction in peak exercise wedge pressure and improvement in peak VO_2, NT-proBNP, and Minnesota Living with HF Score at 6 months follow-up. One-half of patients in the ablation arm no longer met criteria for HFpEF on exercise right heart catheterization at 6 months.[134]

Importantly, while a large body of data supporting use of catheter ablation of AF among patients with HF exists, rhythm control by means of antiarrhythmic drug use is also of benefit. A secondary analysis of EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) found that patients with signs or symptoms of HF (regardless of EF) randomized to early rhythm control had a significantly lower risk of death from cardiovascular causes, stroke, or hospitalization for HF or acute coronary syndrome.[135] Importantly, most patients assigned to rhythm control in that analysis were treated with antiarrhythmic drugs (31% amiodarone, 33% flecainide, 10% dronedarone), and fewer than 10% underwent ablation.[135] Notably, many antiarrhythmic agents are contraindicated among patients with HF because of structural heart disease, coronary artery disease, reduced EF, or NYHA functional class III or IV symptoms, frequently leaving amiodarone as the only available antiarrhythmic drug.[10] In a randomized trial of patients with HFrEF and AF randomized to ablation or amiodarone, patients who underwent ablation had greater freedom from AF, a lower rate of unplanned hospitalization, and decreased mortality.[136]

The mechanism by which rhythm control exerts benefit in HF remains uncertain. Given that BBs may not have the same benefit among patients with HFrEF in AF, one possibility is that rhythm control restores the morbidity- and mortality-lowering benefits of BBs. In CASTLE-AF, the point estimate for the HR for the primary outcome was lower among patients receiving BBs, although it was not statistically different from those not receiving BBs.[131] Similarly, the mortality-lowering benefits of cardiac resynchronization therapy have been shown to be attenuated in the presence of AF,[137] providing another possible mechanism by which rhythm control may improve outcomes. Among patients with permanent AF and concomitant HF (regardless of EF) with at least 1 hospitalization in the preceding year, a strategy of atrioventricular nodal ablation and cardiac resynchronization therapy was shown to improve quality of life, reduce HF hospitalizations, and decrease mortality compared with pharmacologic rate control.[138,139]

CONCLUSIONS

AF is common among patients with HF and is associated with worse outcomes. Many components of GDMT may reduce incident AF among patients with HF. GDMT maintains its morbidity- and mortality-

reducing benefits regardless of AF status among patients with HFrEF, although data are conflicting for whether this statement is true of BBs. Similarly, medical therapies for HFmrEF and HFpEF maintain their beneficial effects in patients with and without AF. Studies have evaluated patients with AF and EF ≥40% as 1 cohort. Thus, although some data suggest that angiotensin receptor-neprilysin inhibitors and SGLT2 inhibitors exert differential benefit across the spectrum of midrange and preserved EFs,[51,140] it is unknown whether this gradient of benefit is present for patients with AF and HFmrEF or HFpEF. There is a large body of evidence suggesting that rhythm control and catheter ablation for AF improves outcomes for patients with HFrEF. Preliminary studies suggest symptomatic and hemodynamic improvements for patients with HFmrEF and HFpEF who undergo AF ablation, though there may be increased AF recurrence and need for repeated ablation among those with HFpEF. Whether catheter ablation reduces cardiovascular endpoints such as HF hospitalization and mortality in HFpEF is being evaluated in the ongoing CABA-HFPEF study (Catheter-Based Ablation of Atrial Fibrillation Compared to Conventional Treatment in Patients with Heart Failure with Preserved Ejection Fraction; NCT05508256).

The development of AF in a patient with HF is both a common occurrence and a significant clinical event associated with poor outcomes. GDMT and rhythm control improve morbidity and mortality in patients with AF and HF across the spectrum of EF. Therefore, clinicians caring for patients with concomitant HF and AF should initiate GDMT and consider a rhythm control strategy.

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