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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

The Increasing Role of Rhythm Control in Patients With Atrial Fibrillation

JACC State-of-the-Art Review

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ABSTRACT

The considerable mortality and morbidity associated with atrial fibrillation (AF) pose a substantial burden on patients and health care services. Although the management of AF historically focused on decreasing AF recurrence, it evolved over time in favor of rate control. Recently, more emphasis has been placed on reducing adverse cardiovascular outcomes using rhythm control, generally by using safe and effective rhythm-control therapies (typically antiarrhythmic drugs and/or AF ablation). Evidence increasingly supports early rhythm control in patients with AF that has not become long-standing, but current clinical practice and guidelines do not yet fully reflect this change. Early rhythm control may effectively reduce irreversible atrial remodeling and prevent AF-related deaths, heart failure, and strokes in high-risk patients. It has the potential to halt progression and potentially save patients from years of symptomatic AF; therefore, it should be offered more widely. (J Am Coll Cardiol 2022;79:1932–1948) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults, with approximately 44 million individuals estimated to have AF or atrial flutter worldwide.[1,2] In addition, there are many patients with undiagnosed AF who often may be first detected after a stroke, development of left ventricular dysfunction, or incidentally.[3,4] AF is associated with substantial mortality and morbidity, which pose a significant burden to patients and health care services.[2]

Management of the condition has evolved over time and there has been a therapeutic paradigm shift away from concentrating solely on prevention of AF recurrence towards ventricular rate control, based on so-called "rate versus rhythm control" randomized trials conducted >2 decades ago.[5-8] With the more recent development of targeted therapies aimed specifically at restoration and maintenance of sinus rhythm with antiarrhythmic drugs (AADs) and left atrial ablation, it became

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HIGHLIGHTS

- AF is the most common adult arrhythmia, associated with substantial patient and health care burden.
- Increasing evidence supports early rhythm control for most patients with recently diagnosed AF as well as for those who are symptomatic.
- A paradigm shift is evolving in favor of rhythm control rather than rate control for patients with new-onset AF.

necessary to re-assess their impact on major adverse cardiovascular outcomes, such as death, stroke, systemic embolism, or progression of heart failure, as well as AF recurrence and quality of life (QoL).[9,10] Results from several subsequent trials and observational studies suggest that optimal rhythm management may be preferable to simple rate control.[11,12]

In the last few years, early intervention with rhythm control in the form of AADs or catheter ablation has shown promising results in maintaining sinus rhythm, and may delay progression of paroxysmal AF to persistent or permanent AF.[12-14] In this article the rationale and evidence for more widespread adoption of early rhythm control in AF management are explored.

CURRENT AF MANAGEMENT

Management comprises 3 main domains summarized in the "ABC" scheme of the 2020 European Society of Cardiology (ESC) atrial fibrillation guidelines; these are "A" for anticoagulation/avoid stroke, "B" for better symptom control using rate and rhythm management, and "C" for therapy of concomitant cardiovascular conditions.[2,15,16]

AADs typically used for restoration and/or maintenance of sinus rhythm are amiodarone, dofetilide, dronedarone, flecainide, propafenone, and sotalol.[2] Pharmacological rate-control strategies aim to regulate ventricular rate during AF with atrioventricular nodal blocking agents, mainly beta-blockers, non-dihydropyridine calcium-channel blockers, digoxin, and occasionally amiodarone.[2] Rarely, atrioventricular node ablation and permanent pacing may be considered.

The current use of rhythm-control therapy is based on evidence generated in key trials originally conducted to compare rhythm vs rate control strategies. These include the following studies: PIAF (Pharmacological Intervention in Atrial Fibrillation), AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management), RACE (Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation), AF-CHF (Atrial Fibrillation and Congestive Heart Failure), STAF (Strategies of Treatment of Atrial Fibrillation), and J-RHYTHM (Japanese Rhythm Management Trial for Atrial Fibrillation) (**Table 1**).[17-22] Overall, few significant differences in important endpoints have been observed between rhythm- and rate-control strategies in these comparison trials (**Table 2**), but meta-analyses have shown that fewer hospitalizations were required to deliver simple rate control.[18-20] As a result, treatment currently defaults to initial rate control, with rhythm control being reserved to improve symptoms that persist despite adequate rate control.[2,16] General AF registries suggest that 75%-85% of patients with AF are not treated with rhythm-control therapy.[23,24]

Not surprisingly, sinus rhythm maintenance was higher in patients receiving rhythm-control therapy than in those receiving rate-control therapy.[20,22] Although the findings from RACE suggest that maintenance of sinus rhythm is less important than concomitant cardiovascular disease in causing cardiovascular events, the ensuing RACE III trial did not find a strong effect of intensive therapy of concomitant cardiovascular conditions after cardioversion on recurrent AF or on outcomes.[25-27] However, effective rhythm control may be beneficial for prevention of severe cardiovascular events in addition to being indicated in patients with prominent symptoms of AF.[19,28]

After prespecified covariate adjustments for baseline characteristics in the AFFIRM trial, there was a trend towards a higher mortality for rhythm control compared with rate control.[18] Similarly, in RACE, mortality tended to be lower with rate control compared with rhythm control, particularly in female patients or those with hypertension, although the overall patient number was small.[19,29,30] Conversely, in a subgroup of patients with no heart failure at baseline in the AFFIRM trial, there was a significantly increased risk of incident heart failure and/or cardiac death in the rate-control arm compared with the rhythm-control arm.[31] Predictors of mortality in AFFIRM were older age, comorbidities, and use of digoxin or AADs, whereas use of anticoagulation and sinus rhythm during follow-up were associated with lower mortality.[32]

In the PIAF, AFFIRM, and STAF trials, fewer patients were hospitalized in the rate-control group

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drugs
AF = atrial fibrillation
ESC = European Society of Cardiology
RCT = randomized clinical trials
QoL = quality of life

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TABLE 1 Study Design of Trials Using Rhythm- and Rate-Control Strategies in Treatment of AF

Trial[a]	N	Follow-Up	AF Classification	Rhythm-Control Strategy[b]	Rate-Control Strategy	Anticoagulation
PIAF[17]	252	1 y	Persistent AF	Amiodarone for 3 wks, cardioversion thereafter if needed. Amiodarone for maintenance. For recurrences, therapy as needed at physician's discretion.	Diltiazem. Additional therapy as needed at physician's discretion.	All patients
AFFIRM[18]	4,060	Mean: 3.5 y; maximum: 6 y	Recurrent non-permanent AF	At physician's discretion: amiodarone (62.8% used at any time), disopyramide (4.3%), flecainide (8.3%), moricizine (1.7), procainamide (8.5%), propafenone (14.5%), quinidine (7.4%), sotalol (41.4%) and combinations of these. Dofetilide could be used once available (0.6%).	At physician's discretion: beta-blockers, calcium-channel blockers (verapamil and diltiazem), digoxin, or combinations of these.	Continuous OAC encouraged in the rhythm-control group, but could be stopped at physician's discretion.[c]
RACE[19]	522	Mean: 2.3 y	Persistent AF or AFL	Electrical cardioversion then AAD therapy with sotalol. Amiodarone, flecainide, and propafenone used for recurrences.	Digitalis, a nondihydropyridine calcium-channel blocker, or a beta-blocker, alone or in combination.	OAC for 4 wks before and 4 wks after cardioversion. OAC could be stopped at 1 mo.[d]
STAF[147]	200	36 mo	Persistent AF	Internal or external cardioversion, with repeated cardioversions for AF recurrence. For prophylaxis of AF recurrence: class I AADs or sotalol[e], or beta-blocker and/or amiodarone.[f]	Beta-blockers, digitalis, calcium antagonists, or AV-nodal ablation/modification with/without a pacemaker.	All patients
AF-CHF[20]	1,376	Mean: 37 mo; maximum 74 mo	History of AF with ECG documentation[g]	Aggressive therapy with AADs and electrical cardioversion within 6 wks of randomization if sinus rhythm not attained. Repeat cardioversions for AF recurrence. Amiodarone for maintenance and sotalol or dofetilide if required. Amiodarone (82%), dofetilide (<1%), and sotalol (2%).	Adjusted doses of beta-blockers with digitalis. AV-nodal ablation with pacemaker recommended if target heart rate not met.	All patients
J-RHYTHM[22]	885	Mean: 578 d	Paroxysmal AF	AADs according to contemporaneous Japanese guidelines.[148] Amiodarone (0.5%), aprindine (7.2%), bepridil (6.7%), cibenzoline (20.8%), disopyramide (8.8%), flecainide (8.1%), pilsicainide (32.5%), pirmenol (1.0%), and propafenone (11.7%).	Beta-blockers, calcium-channel blockers, or digitalis.	All patients[h]

[a]Traditional rhythm vs rate trials. [b]Percentages of patients receiving AADs provided where available and when more than one drug was used in the study. [c]If SR maintained for ≥4, and preferably 12, consecutive weeks with AAD therapy. [d]If SR present at 1 month, OAC could be stopped or changed to aspirin. [e]In the absence of coronary heart disease and in patients with normal LV function. [f]In patients with coronary heart disease or impaired LV function. [g]Defined as 1 episode lasting for ≥6 h or requiring cardioversion within the previous 6 mo or an episode lasting for ≥10 min within the previous 6 mo and previous electrical cardioversion for AF. [h]According to a protocol modified from that used in AFFIRM.

AAD = antiarrhythmic drug; AF = atrial fibrillation; AF-CHF = Atrial Fibrillation and Congestive Heart Failure; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; AFL = atrial flutter; AV = atrioventricular; ECG = electrocardiogram; J-RHYTHM = Japanese Rhythm Management Trial for Atrial Fibrillation; LV = left ventricular; OAC = oral anticoagulation; PIAF = Pharmacological Intervention in Atrial Fibrillation; RACE = Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation; SR = sinus rhythm; STAF = Strategies of Treatment of Atrial Fibrillation.

than in the rhythm-control group.[17,18,21] Similarly, fewer patients randomized to rate-control therapy were hospitalized in AF-CHF, a finding that was significant during the first year of the study.[20] These differences are routinely observed in all these randomized controlled trials (RCTs), as hospitalizations are inherently more likely with rhythm than rate control; this is because of the necessary monitoring during drug dose titration and the high likelihood of re-admissions associated with AAD use such as adverse drug effects and the need for other rhythm-control interventions such as left atrial ablation and cardioversion. When treatment adjustments for rhythm control were excluded, hospitalization rates from the AFFIRM analyses were similar in both cohorts.[33]

In general, rates of stroke, systemic embolism, and major bleeding did not differ between treatment strategies although event-free survival (events comprised total mortality, symptomatic stroke, systemic embolism, major bleeding, heart failure, and physical/psychological disability) was significantly better for rhythm control than rate control ($P = 0.0128$) in the J-RHYTHM trial.[19,22,34,35]

QoL is significantly impaired in patients with AF compared with that of the general population and control groups, including patients with coronary heart disease.[36-38] Despite this, QoL is not always measured in rhythm- vs rate-control trials, and there have been methodological weaknesses such as small sample size, lack of a control group, short-term follow-up periods (<6 months) and use of generic, rather than AF-specific, tools to assess QoL. Furthermore, substudies evaluating QoL, even from the larger trials, may not be sufficiently powered to provide meaningful analyses.[37] Notwithstanding

TABLE 2 Key Outcomes of Trials Using Rhythm- and Rate-Control Strategies in Treatment of AF

Trial	Primary Endpoint	Primary Endpoint Result	Patients in SR
PIAF[17]	Improvement in AF-related symptoms (palpitations, dyspnea, and dizziness)	No significant difference between treatment arms	Rhythm control: 56% at study end Rate control: 10% at study end
AFFIRM[18]	Overall mortality	Rhythm control: 24% at 5-y follow-up Rate control: 21% at 5-y follow-up (NS across follow-up period)	Rhythm control: 62.6% at 5-y follow-up Rate control: 34.6% at 5-y follow-up
RACE[19]	Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, the need for a pacemaker, or severe AEs	Rhythm control: 22.6% at study end Rate control: 17.2% at study end (noninferior, approaching superior)	Rhythm control: 39% at study end Rate control: 10% at study end
STAF[147]	Composite of death, stroke or transient ischemic attack, systemic embolism or cardiopulmonary resuscitation	Rhythm control: 5.54%/y Rate control: 6.09%/year (NS)	Rhythm control: 38% at last follow-up Rate control: 9% at last follow-up
AF-CHF[20]	Death from cardiovascular causes	Rhythm control: 27% at study end Rate control: 25% at study end (NS)	Rhythm control: 73% at 4-y follow-up Rate control: 30% to 41% during follow-up[b]
J-RHYTHM[22]	Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure[a] and physical/psychological disability requiring strategy alteration	Rhythm control: 15.3% at study end Rate control: 22.0% at study end (HR: 0.664; $P = 0.0128$)	Rhythm control: 72.7% at 3 y Rate control: 43.9% at 3 y

[a]Requiring intravenous administration of diuretics. [b]Data reported are patients with AF (59% to 10%).
AE = adverse event; HR = hazard ratio; NS = nonsignificant; SR = sinus rhythm; other abbreviation as in Table 1.

these limitations, the prevailing finding of rhythm- vs rate-control trials, such as RACE and PIAF, is that QoL is observed to improve under both strategies, often with little difference between the two.[39,40] However, the CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial and the RECORD-AF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation) observational trial, as well as large real-world registries such as the ESC-EHRA EORP-AF (ESC-European Heart Rhythm Association EURObservational Research Programme AF General Long-Term Registry), have reported a potential QoL benefit of rhythm control vs rate control.[41-43] Furthermore, when rhythm control therapy is chosen, there are consistent data that AF ablation improves QoL more than AAD therapy, perhaps because of chronotropic incompetence and resulting impairment of effort tolerance due to AAD therapy.[42,44,45] Overall, 2 key lessons have emerged from recent trials. First, even small degrees of AF burden can lead to impairment in QoL, but restoration of sinus rhythm can improve QoL.[46] Second, reductions in AF burden can meaningfully improve QoL and risk of events such as heart failure, even without total freedom from AF.[42,47,48]

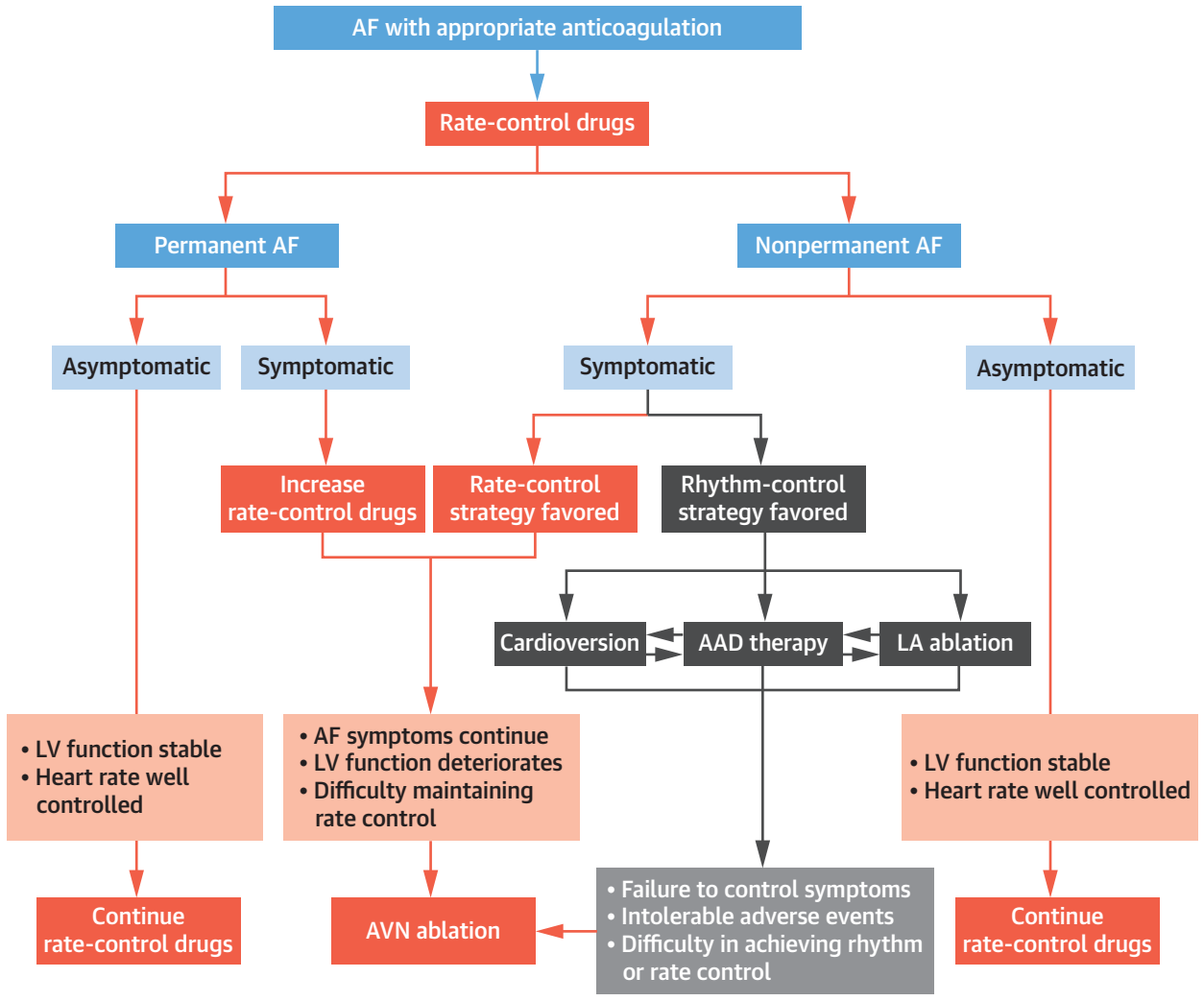
Based on the available evidence, a treatment pattern based on offering initial rate control to most patients has emerged, reserving rhythm control to relatively few patients who remain highly symptomatic (Figure 1). In clinical practice and in AF guidelines published by the ESC, and the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS), rhythm control is added to rate control specifically and primarily to improve symptoms, or in specific patient subgroups who may be expected to benefit from a rhythm-control strategy (Figure 2).[2,15,16]

EVOLUTION OF RHYTHM-CONTROL METHODS

AAD THERAPY FOR RHYTHM CONTROL. Pharmacological therapy for AF evolved substantially, and AAD therapy became a foundation of AF clinical management.[49] Maintenance of sinus rhythm has itself been associated with reductions in death and cardiovascular events.[21,32] In general, AADs approximately double the likelihood of maintaining sinus rhythm compared with no rhythm-control therapy.[50-55] In RCTs, the proportion of patients remaining in sinus rhythm varies, but typically ranges from 36% to 83% for rhythm control and 10% to 61% for rate control.[12,18-20,54,56]

However, despite the clear effects of rhythm-control therapy on maintaining sinus rhythm, RCTs, systematic reviews, and meta-analyses have largely reported no significant difference between rhythm- and rate-control strategies with respect to all-cause

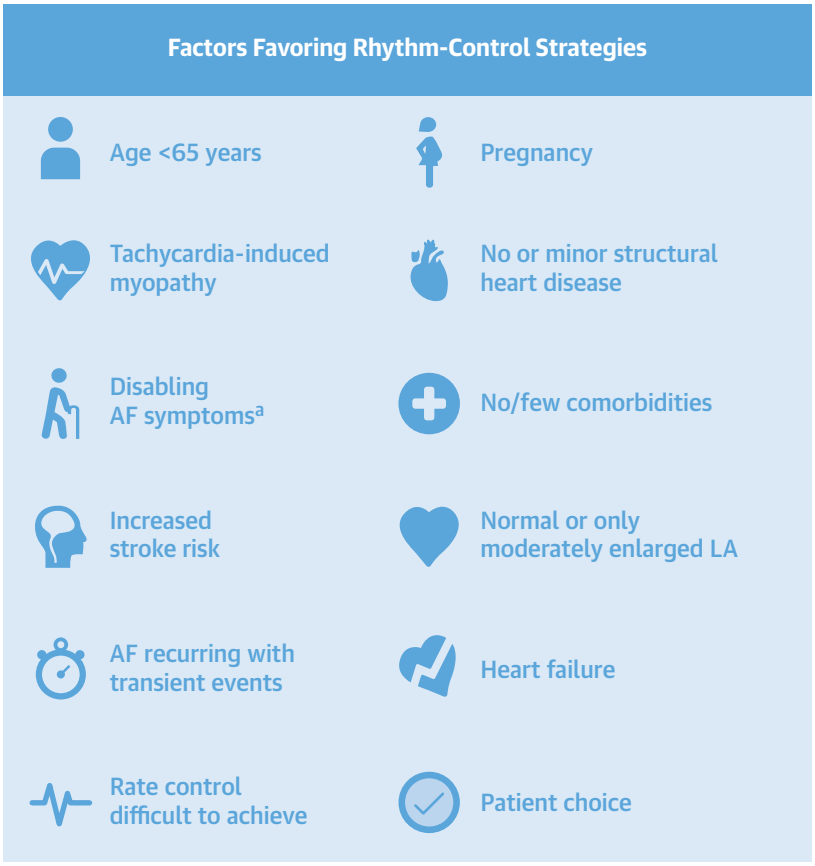
FIGURE 1 Principles of Current Guidelines for Rate/Rhythm Control in AF Management



Current AF management guidelines largely recommend initial rate control, with rhythm control added specifically and primarily to symptomatic patients.
AAD = antiarrhythmic drug; AF = atrial fibrillation; AVN = atrioventricular node; LA = left atrium; LV = left ventricular.

mortality, cardiovascular mortality, stroke, heart failure, and other cardiovascular complications.[5-8,57] Some earlier meta-analyses found trends that favored rate control for reducing risk of death, stroke, and hospitalization.[58,59] However, it is possible that results from these trials conducted in the 1980s and 1990s were affected by the lack of safe and effective therapies, small sample sizes, inclusion of patients with long-standing AF, variable endpoints, less stringent monitoring, inadequate and unbalanced therapies for underlying medical conditions and anticoagulation therapy, unexpected sepsis in the rate-control arm as in AF-CHF, and the use of inappropriately high or suboptimal AAD doses, potentially reducing efficacy or inciting proarrhythmia.[15,20,60,61] In the AFFIRM trial, the high level of patient crossover from rate to rhythm control due to uncontrolled symptoms or heart failure highlights the importance of these aspects in patient management that were not taken into account during the design of that trial.[18] Furthermore, even the longest trials in AF of 5-6 years could be considered to be relatively short compared with the years of potential AF adversity faced by patients with long-standing AF. For example, observational results from Canada also showed little difference in mortality until 4 years post-treatment initiation for rhythm or rate control, after which, long-term results progressively favored

FIGURE 2 **Guideline Recommendations for Rhythm Management in Patients With Nonpermanent AF**



In addition to use primarily in symptomatic patients, rhythm control is also currently often reserved for use in specific patient subgroups who may be expected to benefit from a rhythm-control strategy. [a]As perceived by the patient according to validated tools. Abbreviations as in Figure 1. Adapted from Hindricks et al.[2]

rhythm control, with mortality decreasing in the rhythm-control group after year 5.[62]

Initial enthusiasm for AADs was dampened after their association with excess mortality in patients with prior myocardial infarction, impaired left ventricular function, and ventricular ectopy, likely attributable to their proarrhythmic or negative inotropic effects, in the CAST (Cardiac Arrhythmia Suppression Trial), CAST II, SWORD (Survival With Oral d-Sotalol in Patients With Left Ventricular Dysfunction After Myocardial Infarction), and ALIVE (Azimilide Post-Infarct Survival Evaluation) studies in the 1990s.[63-66] However, this was followed by the evaluation of AADs for rhythm control in patients with AF and the development of more atrial-specific AADs in the early 21st century.[50-54] Furthermore, there has been progress in AF ablation (pulmonary vein isolation), which has been shown to be more effective than AADs in maintaining sinus rhythm, (especially for patients in whom AADs are ineffective) with a good safety record.[67,68]

At the same time, the management of cardiovascular comorbidities underwent considerable change. Some of these changes have directly or indirectly reduced the likelihood of AF, changed the hemodynamic, thrombogenic and electrophysiologic context in which AF occurs, and potentially improved its management and the possible success and safety of rhythm-control therapies. The use of "upstream" therapies (such as mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and sodium-glucose co-transporter-2 inhibitors) has also been shown to be associated with improved maintenance of sinus rhythm.[26,69,70-77] Lifestyle adjustments such as weight loss, increased exercise, and the management

TABLE 3 Study Design and Outcomes of EAST-AFNET 4 and ATHENA Trials

	Trial	
	EAST-AFNET 4[12]	ATHENA[11,104,105]
N	2,789	4,628
Follow-up	Median: 5.1 y	Mean: 21 mo; Maximum: 2.5 y
AF classification	Recent-onset AF (≤12 mo) and at risk for stroke[a]	Paroxysmal or persistent AF or AFL and ≥1 further risk factor
Rhythm control strategy[b]	Early rhythm control: AADs or ablation, as well as cardioversion for persistent AF. AADs: 87.0%; initial therapy: amiodarone (19.6%), dronedarone (16.7%), flecainide (35.9%), propafenone (7.0%), other AAD (7.6%) Ablation 8.0%[c]	Dronedarone
Comparator arm	Usual care: rate control supplemented by rhythm control only in symptomatic patients on adequate rate-control therapy[d]	Placebo/standard care
Anticoagulation	Standard care[d]	Rates of OAC use were similar to those seen in community practice
Primary endpoint	Composite of death from cardiovascular causes, stroke, or hospitalization with worsening heart failure or acute coronary syndrome	First hospitalization due to cardiovascular causes or death from any cause
Primary endpoint result	Occurred less often with early rhythm control than usual care (HR: 0.79; $P = 0.005$)	Dronedarone: 31.9% Placebo: 39.4% (HR: 0.76; $P < 0.001$)
Patients in sinus rhythm	Early rhythm control: 82.1% at 2 y Usual care: 60.5% at 2 y	Dronedarone: 42.9%[e] Placebo: 29.2%[f]

[a]Age >75 years, previous TIA/stroke, or ≥2 of the following criteria: age >65 y, female, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease, or left ventricular hypertrophy. [b]Percentages of patients receiving AADs provided where available and when more than one drug was used in the study. [c]Percentages of patients receiving AADs or ablation do not add up to 100%, as not all randomized patients received therapy. [d]Per guidelines on management of AF.[16,149,150] [e]Proportion of patients who did not have AF/AFL recurrence during the ATHENA trial out of patients who had undergone prior ablation and were in SR at baseline.

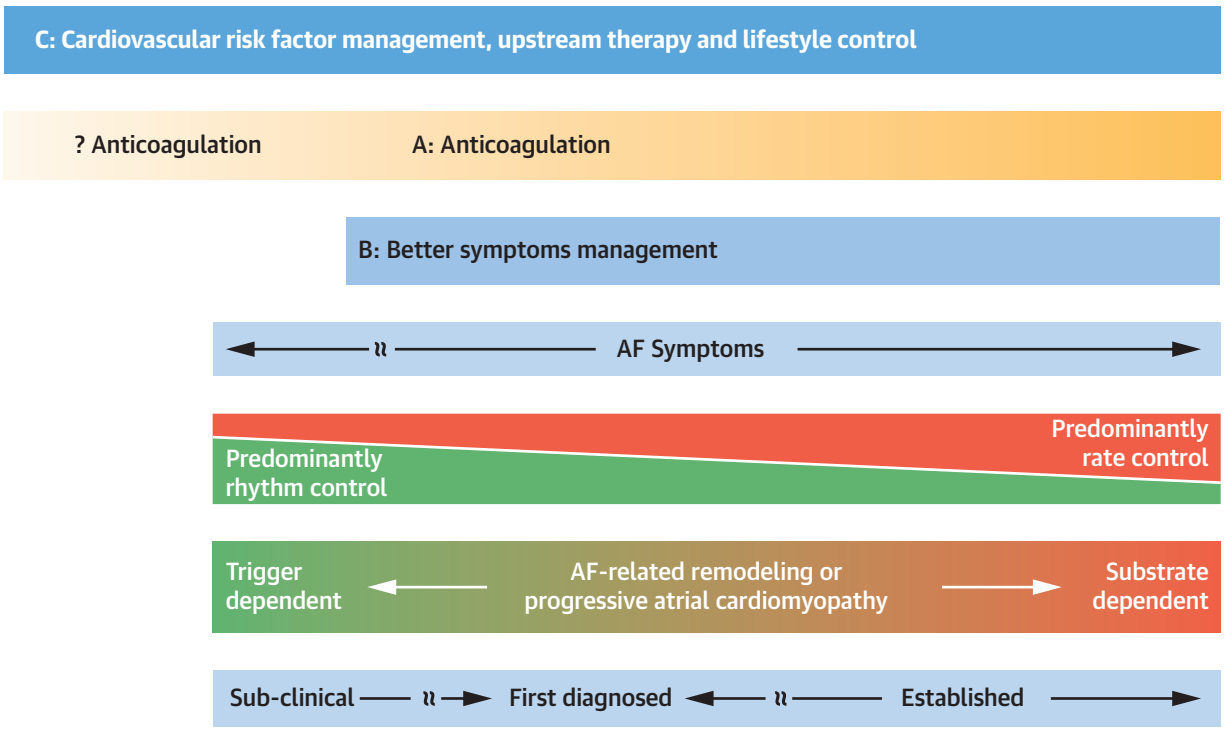
ATHENA = A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with AF/atrial flutter; EAST-AFNET 4 = Early Treatment of Atrial Fibrillation for Stroke Prevention Trial; TIA = transient ischemic attack; other abbreviations as in Tables 1 and 2.

of sleep apnea may also lead to reduction in AF burden.[2] Altogether, these advances form an improved background for successful, contemporary rhythm management. Modern management comprises therapies developed in this new context and includes left atrial ablation and the AAD dronedarone.[11] Regarding dronedarone, studies have shown that this drug is effective in maintaining sinus rhythm in patients who have experienced AF.[78] Although it is less effective than amiodarone in terms of reducing AF recurrence, dronedarone is associated with a better safety profile and is thus supported as a first-line treatment option for rhythm management in various patient populations.[2,79]

AF ABLATION FOR RHYTHM CONTROL. Since the late 20th century, there has been rapid development in ablation, evolving from an experimental procedure to an important treatment option for AF that is recommended in numerous guidelines.[2,15,16,80] Although ablation is accompanied by upfront complications because of its complex interventional nature, which can result in collateral damage to nearby organs and structures, the complication rate has declined in recent years in experienced centers due to quality improvement initiatives and advancement in techniques and technologies.[81,82] Additionally, ablation is more effective than AADs for maintaining sinus rhythm, including when used as first-line treatment for rhythm control.[13,80,83-85]

Early studies of ablation often showed superiority in achieving sinus rhythm compared with pharmacological therapy, although these studies frequently enrolled patients with symptomatic AF who had previously failed AAD therapy, creating a potential bias.[45,86-92] When investigating the efficacy of ablation in rhythm-control-naïve patients, however, the RAAFT (Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation Trial) and RAAFT-2 trials showed that AF recurrence occurred in significantly fewer patients in the ablation group than in the AAD group (13% vs 63%, respectively, and 55% vs 72%, respectively).[93,94] The longer-term MANTRA-PAF (Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) study, which also included patients with symptomatic paroxysmal AF who had not received previous AAD therapy for AF, randomized patients to radiofrequency ablation or AAD therapy.[83] Although no significant difference in the cumulative AF burden (primary endpoint) was found between treatment arms across the 24-month

FIGURE 3 **Rhythm Management in AF and Underlying Progression of Atrial Cardiomyopathy/Remodeling**



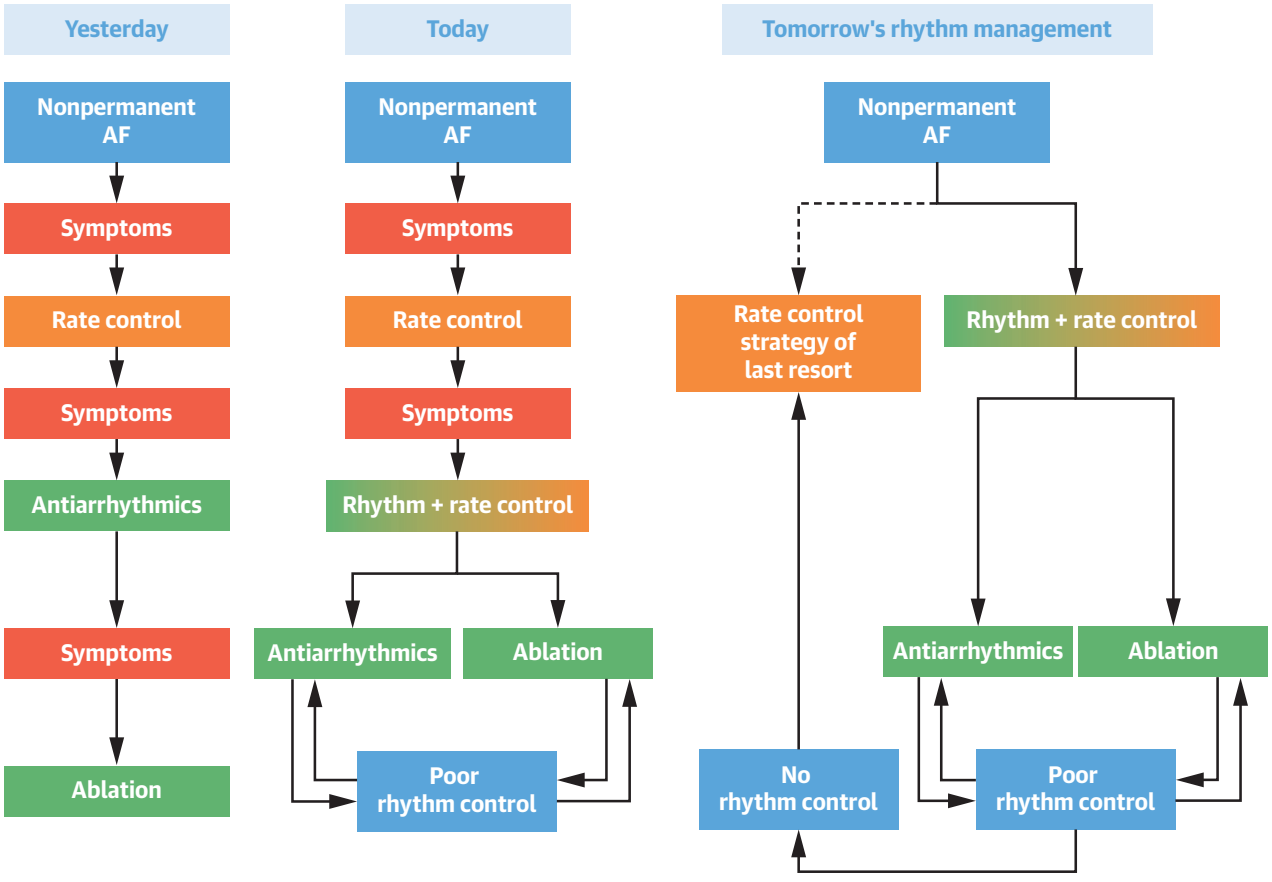
Currently, rhythm control is recommended only after the development of refractory AF symptoms, which may be too late to prevent AF progression. Increasing evidence supports rhythm control as an important strategy in the early stages of AF in combination with rate control and upstream therapies, as outlined by the Atrial fibrillation Better Care ("ABC") holistic pathway (A: anticoagulation/avoid stroke; B: better symptom management; C: cardiovascular and comorbidity optimization).[2] Importantly, management of lifestyle and comorbidities should begin well before AF manifestation in those at risk. Anticoagulation should be initiated as early as possible after AF onset and is sometimes initiated before AF onset when there is an underlying comorbidity requiring anticoagulation or short bursts of atrial tachyarrhythmia insufficient for formal diagnosis of AF at risk of stroke. AF-related symptoms which guidelines recommend to decide on therapy can occur at any stage after AF onset. Abbreviation as in Figure 1.

trial period, the AF burden was lower for the ablation arm at the 24-month time point than for the AAD arm ($P = 0.007$). In addition, more patients in the ablation arm compared with the AAD-treated arm were free from any AF (85% and 71%, respectively; $P = 0.004$) and from symptomatic AF (93% and 84%, respectively; $P = 0.01$) at 24 months.[83] These observations were repeated at the 5-year follow-up, when the cumulative AF burden was lower for both groups vs baseline but significantly lower in the ablation than in the AAD group.[68]

Results from the later CAPTAF (Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation), CABANA, AATAC (Ablation vs Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device), and CASTLE-AF (Catheter Ablation vs Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trials have shown that ablation can significantly reduce the burden of AF and frequency of AF recurrence compared with pharmacological rhythm-control treatment.[44,47,87,93-95]

In CABANA, the primary composite endpoint of death, disabling stroke, serious bleeding, or cardiac arrest was not different between the ablation and pharmacological-therapy arms. Also, the proportion of patients who had persistent or long-standing AF was reduced from approximately 57% across both arms at the start of the trial to 16% in the ablation arm vs 26% in the pharmacological-therapy arm, showing that ablation can benefit patients with long-standing AF.[67] AF ablation was associated with lower AF recurrence rates than pharmacological therapy (37% vs 58%, respectively, at 1-year follow-up and 50% vs 69%, respectively, at 3-years follow-up), concordant with other ablation trials. However, 17.1% of patients required a repeat ablation procedure during

CENTRAL ILLUSTRATION **Summary of the Evolution of Atrial Fibrillation Rhythm Management**



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Early atrial fibrillation (AF) treatment strategies (Yesterday) focused on escalation from initial rate control to rhythm control for those patients with persistent AF symptoms, reserving ablation as a late-stage intervention. More recent guidelines (Today) recommend a combination of rhythm and rate-control strategies for symptomatic patients, should adequate control not be achieved with first-line rate-targeting therapies. Our recommended treatment paradigm (Tomorrow's rhythm management) places rhythm control in a more prominent position within the rhythm management of AF, as a first-line therapy in combination with atrioventricular nodal therapy (rate control) for the majority of patients, with ablation as an important early treatment approach.

post-blanking follow-up, showing that ablation should not be seen as a one-off curative treatment for AF.[67,95,96] Thus, CABANA confirms that AF ablation prevents recurrent AF more effectively than AAD therapy in a population of patients with established AF and concomitant cardiovascular conditions.[96]

Small early ablation studies in patients with heart failure showed not only efficacy in terms of restoration of sinus rhythm but also improvement of left ventricular ejection fraction, even in patients with previously good ventricular rate control, and ablation has generally been superior to antiarrhythmic drug therapy in these patients.[97,98] In the multicenter AATAC study, patients with persistent AF and coexistent heart failure were randomized to catheter ablation or amiodarone therapy. At 2 years of follow-up, catheter ablation was superior to pharmacological treatment in achieving freedom from AF, reduced unplanned cardiovascular hospitalization and mortality, and substantial improvement in left ventricular ejection fraction, 6-minute walk distance, and QoL.[47]

In CASTLE-AF, patients with coexisting AF and heart failure were assigned to catheter ablation or pharmacological rate-control therapy, with the former found to be associated with a reduced AF burden and an improved left ventricular ejection fraction compared with pharmacological treatment.[99]

Furthermore, the composite primary endpoint (death or hospitalization for worsening heart failure) occurred in significantly fewer patients in the ablation group than in the pharmacological therapy group ($P = 0.006$). However, some have expressed concerns regarding methodological problems of this trial, such as small number of endpoint events, exclusion of patients from the intention-to-treat analysis, and patients with missing follow-up data.[100] Improvement of left ventricular function after AF ablation appears to be consistent across several randomized trials.[101]

These studies, in addition to the more recent STOP-AF (A Clinical Study of the Arctic Front Cryoablation Balloon for the Treatment of Paroxysmal Atrial Fibrillation), EARLY-AF (Early Aggressive Invasive Intervention for Atrial Fibrillation) trial, and CRYO-First (Cryoballoon catheter ablation vs AADs as a first-line therapy for patients with paroxysmal atrial fibrillation) trials provide important evidence showing that AF ablation is as safe as AAD therapy, and more effective in maintaining sinus rhythm when used as first-line rhythm control therapy in symptomatic patients with AF.[13,85,89] Support of ablation as an effective therapeutic option in AF has been consistently shown in meta-analyses of trials exploring the impact of ablation on a range of hard clinical outcomes beyond AF recurrence.[102,103] Although individual trials included in these analyses were relatively small, together they showed a clear benefit of ablation compared with pharmacological intervention, with significant reductions in mortality, stroke, and hospitalization, particularly within the setting of congestive heart failure.

NEW EVIDENCE SUPPORTING EARLY RHYTHM MANAGEMENT

Although AAD development had been largely concerned with the eradication of AF, safety was also an important issue. When a drug was developed solely as an atrial antiarrhythmic, it became necessary to design an RCT to document safety and to establish potential efficacy with regard to major cardiovascular outcomes in patients with AF. The ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with AF/atrial flutter) trial was conducted in 2005-2006 and remains the largest RCT of antiarrhythmic therapy in AF to date. A primary outcome of death or cardiovascular hospitalization was evaluated in 4,628 patients receiving dronedarone or placebo, both in addition to standard therapy including rate control (**Table 3**).[11] Patients included in the trial had paroxysmal or persistent AF or atrial flutter within 6 months before randomization and met ≥1 $CHADS_2$ risk factors, left ventricular ejection fraction ≤40%, or left atrial enlargement.[11] The majority of patients received oral anticoagulants (OACs) and rate-control therapy.[11,104] Other AAD therapy was not permitted and AF ablation was rarely used, rendering the control arm in ATHENA a rate control arm.[105] Treatment with dronedarone reduced the risk of a primary outcome of hospitalization due to unexpected cardiovascular events or death from any cause compared with placebo.[11,106] Furthermore, there was a notionally significant reduction in secondary outcomes with dronedarone compared with control, including cardiovascular death (secondary outcome) and stroke (post hoc analysis).[11,104]

Although it was shown in ATHENA that potential rhythm control resulted in better cardiovascular outcomes than standard care relying on rate control, the trial also demonstrated that dronedarone was a safe therapy for the ATHENA population.[11] Observational data capturing routine care replicate a lower risk of hospitalization for cardiovascular events, a composite outcome of cardiovascular hospitalization/death from any cause, and a lower risk of ventricular proarrhythmia for patients receiving dronedarone compared with other AADs.[107,108] These beneficial effects of dronedarone have also been seen in patients with AF and coronary heart disease, and in those who underwent AF ablation before enrollment in the trial.[12,105,109] However, in hospitalized patients with new or unstable heart failure with a reduced ejection fraction, and in patients with high-risk permanent AF or flutter, dronedarone was associated with adverse outcomes.[110,111]

CLINICAL BENEFIT OF EARLY RHYTHM MANAGEMENT. Equally important to recognizing the benefit of rhythm-control strategies for a wide range of patients is understanding the importance of early adoption of this approach. Early rhythm-control treatment in patients who have experienced a first AF episode or have recent-onset or paroxysmal AF has shown very promising results over and above the benefits of rhythm control itself.[13,67,84,112] It has been suggested that the self-perpetuating effect of AF through structural remodeling of the atria underlines the importance of treating AF early to potentially halt progression and aid in maintenance of sinus rhythm.[113-115] As just several days or weeks of arrhythmia can cause such atrial changes, early restoration of sinus rhythm could possibly prevent

this potentially irreversible damage and reduce the risk of stroke that is increased even with short episodes of asymptomatic AF.[115,116] Data from the ATHENA trial and observational data from RECORD-AF have shown a lower likelihood of progression to permanent AF using a rhythm-control vs rate-control strategy.[56,117]

The EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) study in patients with AF diagnosed within 12 months before randomization who were at risk of stroke (**Table 3**) has recently been published in support of early comprehensive AF treatment, altering the view on early rhythm control as a general treatment concept.[12] In the study, patients were randomized to usual guideline-recommended care (primarily rate control plus OACs with rhythm control added to control symptoms as per ESC and AHA/ACC/HRS guidelines) or guideline-recommended care plus early rhythm-control treatment, consisting typically of AAD therapy, or, to a lesser degree, ablation, initiated directly after randomization.[2,15,16,118] The first primary outcome was a composite of death from cardiovascular causes, stroke (ischemic or hemorrhagic), or hospitalization with worsening heart failure or acute coronary syndrome, which was reduced by 21% in patients assigned to early rhythm control compared with usual care ($P = 0.005$).[12] Each component of the first primary outcome was numerically less common in patients randomized to early rhythm control compared with usual care whereas there was no difference in the second primary outcome of number of nights hospitalized per year between the strategies.[12] Furthermore, the primary safety outcome (death, stroke, or serious adverse events related to rhythm-control therapy) was not different between randomized groups. Compared with those assigned to usual care, the occurrence of stroke was reduced by approximately one-third and total mortality was 16% lower in patients randomized to early rhythm control.[12] Serious adverse effects related to rhythm control therapy were more common in patients receiving early rhythm-control treatment than usual care, but occurred infrequently, as also seen in the STOP-AF First and CABANA trials, where many of the adverse effects previously associated with AADs were not reported.[12,42,84]

A recent subanalysis of the EAST-AFNET 4 trial in patients with heart failure (predominantly those with preserved ejection fraction) showed that the first primary outcome occurred less often in patients receiving early rhythm-control therapy vs usual care, with the primary safety endpoint occurring in 17.9% of participants in the early rhythm-control therapy group compared with 21.6% in the usual care group.[119] Furthermore, promising results were also seen in a subanalysis stratifying treatment effects in EAST-AFNET 4 according to symptomatic status.[120] These data showed a consistent beneficial effect of early rhythm control vs usual care, independent of whether the patient was symptomatic or asymptomatic. A treatment effect was observed against the primary outcome of 0.77 (95% CI: 0.57-1.03) in asymptomatic patients, 0.84 (95% CI: 0.66-1.09) in those with mild or moderate symptoms, and 0.68 (95% CI: 0.47-099) in those with severe symptoms (P for interaction = 0.743).[120]

As found in the PIAF, AFFIRM and RACE studies, no difference was found in QoL scores for the 2 strategies in the EAST-AFNET 4 study.[12] This was expected as symptom-guided rhythm-control therapy was part of usual care as per AF guidelines at the time and per current AF guidelines.[2,121] However, in contrast to AFFIRM and RACE, stroke occurred less frequently in the early rhythm-control group than in the rate-control group.[12] The use of amiodarone and dronedarone as AAD options in EAST-AFNET 4 and the availability of AF ablation in patients who failed AAD therapy may have contributed to this outcome given that they can be safely used in patients with structural heart disease.[10] In AFFIRM and RACE, sotalol was commonly used, with amiodarone available in both trials, and flecainide and propafenone administered following AF recurrence in RACE.

As a reaction to the findings of EAST-AFNET 4, further analyses exploring the importance of prompt AF treatment initiation have been performed. In the AFFIRM trial, patients diagnosed with AF within 6 months of study enrollment showed no difference in survival, cardiovascular hospitalization, or ischemic stroke between rate and rhythm-control strategies, suggesting the importance of early initiation of treatment, regardless of strategy.[122] In support of this, initiation of either therapy ≤1 year of diagnosis was associated with a lower risk of the primary composite outcome of death from cardiovascular causes, ischemic stroke, admission to hospital for heart failure, or acute myocardial infarction in a nationwide health care database analysis based in Korea, replicating the beneficial effects seen in the EAST-AFNET 4 trial.[123] Another analysis in patients from the ESC-EHRA EORP-AF registry meeting EAST-AFNET 4 eligibility criteria showed a similar effect, although the association did not fulfil rigorous statistical testing, potentially due to the relatively young age of the population and the relatively small number

of patients.[43] Confirmatory observations were made in Optum, a large American health care database and in the National databases of Korea and Taiwan.[123-126] Importantly, these routine health data analyses confirmed the safety of early rhythm-control therapy.[43,123,125,126]

Overall, the benefits of early rhythm control have been shown for both pharmacological therapy and ablation, which are both highly effective when used in recent-onset AF.[80,104,113,116,127,128] Among pharmacological therapies, dronedarone has been the most extensively studied AAD in terms of rhythm control and adverse cardiovascular outcomes in non-permanent AF, particularly in the ATHENA trial.[10,11] Post hoc analyses by AF duration in this trial suggested that the effect of dronedarone was more robust among patients with short (<3 months) and intermediate (≥3 months to <24 months) AF/atrial flutter history than those with longer (≥24 months) history.[112] However, dronedarone should not be used in patients with permanent AF, heart failure with reduced ejection fraction or patients with recent heart failure decompensation/hospitalization. In a recent meta-analysis, patients with a shorter (≤1-year) vs longer (>1-year) diagnosis-to-ablation time were shown to have lower risk of AF recurrence.[129] Results from the ATTEST (Atrial Fibrillation Progression Trial) showed that early ablation as part of standard care was superior to AAD therapy alone in delaying progression from recurrent paroxysmal AF to persistent AF, with the effect apparent at 1 year of follow-up and maintained over 3 years.[14] Similar robust benefits of ablation as a first-line therapy have been seen across a range of trials, and as a result of the recent STOP-AF First study investigating outcomes of cryoballoon ablation when used as initial therapy in patients with paroxysmal AF naïve to rhythm-control therapy, the technique has recently been approved as a first-line therapy for AF in the United States.[13,83,84,85,89] Analyses from CASTLE-AF, CABANA, and other studies supported early ablation in patients with AF and heart failure to prevent progression, as greater improvements in clinical outcomes were observed for patients in lower functional classes of heart failure.[130] Further analyses are required to fully assess whether AF progression to more persistent forms can be prevented by early rhythm control, in addition to lowering the risk of adverse cardiovascular outcomes.

Although catheter left atrial ablation may be the single best therapy, resources do not allow it to be used for all comers. AAD therapy must be improved and catheter ablation must be simplified to improve the clinical value of rhythm control. Academia and the pharmaceutical industry continue to search for more effective and safe AADs such as small-conductance calcium-activated potassium (SK) channel inhibitors, TWIK-related acid-sensitive potassium channel (TASK-1) inhibitors, slow sodium channel inhibition and multichannel inhibitors, and alternative ablation approaches such as pulsed field ablation or electroporation.[131-136] Improvements in surgical therapy are being increasingly explored for the more refractory cases.[137]

In real-world clinical practice, prompt treatment initiation may be hindered by the often asymptomatic nature of early AF. However, informal screening programs and the advent of mobile health devices such as smartwatches have shown increased AF detection rates.[138] One systematic review identified that single time point screening in the general ambulatory population has the potential to identify 1 new treatable case of AF in every 83 people aged ≥65 years screened.[139] Furthermore, exploiting pulse data captured by wearable sensors such as increasingly ubiquitous smartwatches can facilitate highly scalable AF detection and, as a result of ongoing investigation in this area, several mobile health devices have recently received U.S. Food and Drug Administration clearance for clinical use in AF detection.[138,140,141] This may lead to an explosion of early but often asymptomatic cases of AF. Their best management has yet to be fully explored, but their identification will afford an opportunity to tackle the disease at a very early stage and to develop schemes, such as those involving clinical scores or artificial intelligence to assess which form of rhythm management should be considered.[142,143]

CONCLUSIONS

Encouraging results from recent trials support rhythm control as a potentially important strategy in the early stages of AF, which could be a major step towards minimizing the burden of AF for both individuals and for global health care services (**Figure 3**). As a result, there is a paradigm shift well underway (**Central Illustration**) towards offering early rhythm control to all patients with recently diagnosed AF, which is not yet reflected in current guidelines. Concomitant rate control may also be needed until (or unless) rhythm control is fully effective; rate control without concomitant rhythm-control therapy in patients refractory to rhythm control is better thought of and described as an end-stage strategy for rate-control management.

Evidence supports early intervention in all patients with AF that has not become long-standing, where it

may be effective in reducing irreversible structural atrial cardiomyopathy, unmanageable symptoms, and/or strokes in patients at risk. Rhythm control also continues to fulfil an important role in controlling symptoms in those with more advanced AF and may be preferable in younger patients and patients at risk of stroke. In patients with AF and heart failure, catheter ablation may be preferred to AADs due to challenges in optimizing pharmacological strategy in this population.[2]

Given its possible benefits, the attainment and maintenance of sinus rhythm is widely thought to be an important goal in AF treatment. The continued evolution of AF treatment will result in AADs with a better safety profile than previous AADs, and improved ablation therapy may not only reduce but also virtually eliminate AF recurrences, especially when delivered early in the course of the disease.[2,144] A better understanding of the mechanisms initiating AF will also improve long-term success of rhythm control.

Based on available evidence from early RCTs and registries, the primary goals for rhythm control has previously been to reduce AF-related symptoms, including those revealed by exercise intolerance and post-cardioversion, and to improve QoL in patients with AF.[2] However, current practice is moving towards offering rhythm control, not only for persistent symptoms, but also to reduce the risk of adverse cardiovascular outcomes in patients with new-onset and recently-diagnosed AF.[2,16,145,146] Early therapy for AF is not only a possibility but is becoming necessary as informal medical screening and lay detection of AF become increasingly common.

Given the opportunities to reduce AF burden and halt progression that rhythm-control therapy affords, rhythm control should be offered more widely to avoid condemning a patient to a potential for many years of symptomatic AF and obligatory anticoagulation.

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