Clinical Update on the Management of Atrial Fibrillation

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Atrial fibrillation (AF) is a cardiac arrhythmia associated with significant morbidity and mortality, affecting more than 3 million people in the United States and 1–2% of the population worldwide. Its estimated prevalence is expected to double within the next 50 years. During the past decade, there have been significant advances in the treatment of AF. Studies have demonstrated that a rate control strategy, with a target resting heart rate between 80 and 100 beats/minute, is recommended over rhythm control in the vast majority of patients. The CHA_2DS_2–VASc (congestive heart failure, hypertension, age $\geq$ 65 yrs, diabetes mellitus, stroke or transient ischemic attack, vascular disease, female gender) scoring system is a potentially useful stroke risk stratification tool that incorporates additional risk factors to the commonly used $CHADS_2$ (congestive heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, stroke transient ischemic attack) scoring tool. Similarly, a convenient scheme, termed HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly), to assess bleeding risk has emerged that may be useful in select patients. Furthermore, new antithrombotic strategies have been developed as potential alternatives to warfarin, including dual-antiplatelet therapy with clopidogrel plus aspirin and the development of new oral anticoagulants such as dabigatran, rivaroxaban, and apixaban. Vernakalant has emerged as another potential option for pharmacologic conversion of AF, whereas recent trials have better defined the role of dronedarone in the maintenance of sinus rhythm. Finally, catheter ablation represents another alternative to manage AF, whereas upstream therapy with inhibitors of the renin-angiotensin-aldosterone system, statins, and polyunsaturated fatty acids could potentially prevent the occurrence of AF. Despite substantial progress in the management of AF, significant uncertainty surrounds the optimal treatment of this condition.

Key Words: atrial fibrillation, new anticoagulants, rate versus rhythm, antiarrhythmic drugs, upstream therapy, catheter ablation.

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Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting more than 3 million people in the United States.[1] By 2050, the prevalence is estimated to affect more than 7.5 million people.[1] AF is also associated with significant morbidity and mortality, including 20% of all strokes, 33% of hospitalizations related to cardiac arrhythmias, and a 2-fold increased risk of death.[2–4] Taken together, AF remains a significant burden to society and thus represents an area of ongoing research.

Pharmacotherapy for AF consists of two major management decisions: choosing a rate or rhythm control strategy and determining the degree of antithrombotic therapy necessary based on thromboembolic risk.[2, 5] Although substantial progress has been made in the management of AF during the past decade, questions remain regarding the optimal treatment of this condition. In one international survey of more than 10,000 patients, AF was inadequately controlled, with control defined

as either sinus rhythm or AF with a heart rate (HR) of 80 beats/minute (bpm) or less, in 41%.[6] As a result, a review of recent developments in AF should assist clinicians in the management of this condition. To describe the current literature on the treatment of AF, we conducted a MEDLINE search of the English language literature (1950–2009) to identify studies that pertain to the treatment of patients with AF. In this review, we provide an update on rate versus rhythm control strategies, ventricular rate targets, new and emerging antithrombotic strategies and antiarrhythmic drugs, and the use of upstream therapy and ablation in the management of patients with AF.

Rate Versus Rhythm Control

An area of ongoing controversy in AF has been the use of rate or rhythm control strategies. During the past decade, several studies have assessed rate versus rhythm control (Table 1), demonstrating that rate control is not inferior to rhythm control with respect to long-term clinical outcomes, even among older patients with comorbid cardiovascular disease.[7–13] In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, the largest trial to date comparing rate versus rhythm control, the rate of hospitalizations was significantly higher among patients in the rhythm control arm (80.1% vs 73.0%, $p<0.001$), as were adverse effects including torsade de pointes, pulmonary events, gastrointestinal events, bradycardia, and QT prolongation events.[8] Similar results were seen among patients with heart failure (HF), where no significant difference in cardiovascular mortality was observed between the rate control and rhythm control groups, whereas patients assigned to rhythm control experienced a higher rate of hospitalizations (46% vs 39%, $p=0.001$) and required more cardioversions (59% vs 9%, $p<0.001$).[12]

However, a post hoc analysis of the AFFIRM trial (mean follow-up of 3.5 yrs) demonstrated that although antiarrhythmic drugs were associated with a 49% increase in all-cause mortality, maintenance of sinus rhythm was associated with a 53% mortality reduction.[14] Similarly, in a substudy of the Danish Investigations of Arrhythmia & Mortality on Dofetilide (Tikosyn) in Congestive Heart Failure (DIAMOND-CHF) trial (mean follow-up of 1 yr), sinus rhythm was associated with a reduction in mortality (risk ratio 0.44, $p<0.0001$), but the mortality rate between the dofetilide and placebo groups was not significantly different ($p<0.05$).[15] These analyses suggest that if efficacious methods for maintaining sinus rhythm were available with fewer deleterious effects, they might be beneficial.

In the meantime, rate control is currently recommended as the therapy of choice in the majority of patients with AF.[2, 5] It is especially preferred in patients older than 65 years and in those with significant comorbid cardiovascular disease. Rhythm control may be considered in patients who remain symptomatic despite adequate rate control and in those who cannot achieve adequate rate control, either due to medication adverse effects or to inability to achieve ventricular rate control with maximally tolerated doses. Also, young symptomatic patients may benefit from rhythm control; only older individuals were studied in rate versus rhythm control trials.

Ventricular Rate Targets

Previous guidelines for the management of AF have proposed a target resting HR of 60–80 bpm and 90–115 bpm during moderate exercise.[5] Until recently, recommendations for ventricular rate targets were based on only limited evidence, including short-term hemodynamic benefits rather than long-term outcomes.

In a randomized noninferiority trial, the Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (RACE II) trial, investigators compared lenient (resting HR < 110 bpm) and strict (resting HR < 80 bpm) rate control in 614 patients with permanent AF.[16] β-Blockers, nondihydropyridine calcium channel blockers, and digoxin were used to reach target HRs. The primary end point was a composite of cardiovascular death, hospitalization for HF, stroke, systemic embolism, major bleeding, and arrhythmic events.

After nearly 3 years of follow-up, 12.9% of patients in the lenient group and 14.9% of

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Table 1. Summary of Rate vs Rhythm Control Trials in Patients With AF

Trial	Design	No. of Patients	Mean Age (yrs)	Mean Follow-up Period (yrs)	Pertinent Inclusion Criteria	Primary End Point	No. (%) of Patients Reaching Primary End Point		
							Rate Control	Rhythm Control	p
PIAF[7] (2000)	UB, R, P, MC	252	61.0	1.0	Persistent AF (7–360 days)	Symptomatic improvement	76/125 (60.8%)	70/127 (55.1%)	0.32
AFFIRM[8,a] (2002)	UB, R, P, MC	4060	69.7	3.5	Paroxysmal or persistent AF, age > 65 yrs, increased risk for stroke or death	All-cause mortality	310/2027 (25.9%)	356/2033 (26.7%)	0.08
RACE[9] (2002)	UB, R, P, MC	522	68.0	2.3	Persistent AF or atrial flutter, 1–2 cardioversions over 2 yrs, oral anticoagulation	Composite: cardiovascular death, CHF, severe bleeding, pacemaker implantation, thromboembolic events, severe adverse effects of antiarr hythmic drugs	44/256 (17.2%)	60/266 (22.6%)	0.11
STAF[10] (2003)	UB, R, P, MC	200	66.0	1.6	Persistent AF, NYHA class II–IV HF, LVEF < 45%	Composite: overall mortality, cerebrovascular complications, CPR, embolic events	10/100 (10%)	9/100 (9.0%)	0.99
HOT CAFE[11] (2004)	UB, R, P, MC	205	60.8	1.7	Persistent AF	Composite: death, thromboembolic events, intracranial or major hemorrhage	1/101 (1.0%)	4/104 (3.9%)	> 0.71
AF-CHF[12] (2008)	UB, R, P, MC	1376	66	3.1	LVEF < 35%, symptomatic HF	Cardiovascular death	175/694 (25%)	182/682 (27%)	0.59
J-RHYTHM[13] (2009)	UB, R, P, MC	823	64.7	1.6	Paroxysmal AF	Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for CHF, or physical or psychological disability	89/404 (22.0%)	64/419 (15.3%)	0.012

AF = atrial fibrillation; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; CHF = congestive heart failure; CPR = cardiopulmonary resuscitation; DCC = direct current cardioversion; HOT CAFE = HOw to Treat Chronic Atrial Fibrillation; J-RHYTHM = Japanese RHYTHM Management Trial for Atrial Fibrillation; LVEF = left ventricular ejection fraction; MC = multicenter; NYHA = New York Heart Association; P = prospective; PIAF = Pharmacological Intervention in Atrial Fibrillation; R = randomized; RACE = RAte Control vs Electrical cardioversion for persistent atrial fibrillation; STAF = Strategies of Treatment of Atrial Fibrillation; UB = unblinded.

[a]Values are reported from the original publication, which were derived from a Kaplan–Meier analysis. Data have been truncated at 5 years.

Adapted from reference 2.

patients in the strict-control group reached the primary end point (p=0.001), which met noninferiority criteria. The resting HR was achieved in 97.7% of patients in the lenient group and in 75.2% of patients in the strict-control group (p<0.001). In addition, 684 visits were required to achieve the rate target in the strict-control group, whereas only 75 visits were required in the lenient group (p<0.001). Overall, the results of RACE II led the authors to conclude that lenient control is just as effective as strict control and is more convenient.

On closer examination, several limitations may limit the applicability of this trial to many patients with AF. First, the study enrolled a low-risk population; less than two-thirds of patients were symptomatic at baseline and the mean $CHADS_2$ (congestive heart failure, hypertension, age $\geq$ 75 yrs, diabetes mellitus, previous stroke or transient ischemic attack [scoring system]) score was 1.4, with nearly 60% having a $CHADS_2$ score of 1. Of patients with HF, the majority were in New York Heart Association (NYHA) functional class I or II. Second, only a median 9-bpm difference in HR was observed between the lenient and strict-control groups at the end of study. Moreover, the mean resting HR was 85 $\pm$ 14 bpm in the lenient control group and 76 $\pm$ 14 in the strict-control group; thus, both groups were significantly below the lenient threshold.

Based on the results of the RACE II trial, updated practice guidelines recommend a lenient rate control strategy (i.e., a resting HR < 110 bpm) in patients with persistent, asymptomatic AF who have ejection fraction > 40%.[17] If lenient rate control strategy is selected in these patients, monitoring of left ventricular function is recommended. However, because nearly 80% of patients in both groups achieved a resting HR between 80 and 100 bpm, a ventricular rate target between 80 and 100 bpm may also be sufficient,[16] including in patients with symptomatic AF. In patients with symptomatic HF, the lowest tolerated HR (resting HR < 80)[12] may be considered; however, rhythm control should also be considered in patients who remain symptomatic despite adequate rate control.

Risk Stratification for Stroke and Bleeding

CHA_2DS_2-VASc Scheme to Assess Risk of Stroke

Since 2001, the most widely used tool for determining the risk of thromboembolism in patients with AF has been the $CHADS_2$ scoring system.[18] Patients with a $CHADS_2$ score of 2 or greater are considered high risk, thereby warranting oral anticoagulation (OAC).[19] A score of 1 indicates intermediate risk, and guidelines recommend OAC over aspirin, whereas a score of 0 indicates low risk and no antithrombotic therapy is recommended. If antithrombotic therapy is used in patients with a $CHADS_2$ score of 0, aspirin alone is preferred over OAC or dual-antiplatelet therapy. The major advantage of this scoring tool is its ease of use, allowing clinicians to quickly evaluate the most appropriate type of antithrombotic therapy required.

In addition to $CHADS_2$, a number of risk stratification tools have been proposed that vary in complexity.[19] Recently, the CHA_2DS_2-VASc scoring system has been introduced as a strategy to more accurately risk-stratify patients with AF (Table 2).[20] Compared to $CHADS_2$, the new scoring system adds sex and history of vascular disease and stratifies age into two categories (65–74 and $\geq$ 75 yrs of age). A review of this new scoring system, including its merits and limitations, has been discussed recently, so a summary is provided here.[21]

The authors of the CHA_2DS_2-VASc system found that it had improved predictive ability (*C* statistic of 0.606) compared with $CHADS_2$ (*C* statistic of 0.561) and thus advocate its use in patients with AF.[20] In addition to its greater predictive ability, another advantage of CHA_2DS_2-VASc is that it assigns fewer individuals to the intermediate-risk group, thus resulting in more patients receiving the benefits of OAC.

The use of CHA_2DS_2-VASc is recommended in the 2010 European guidelines, specifically when the $CHADS_2$ score is either 0 or 1.[2] If the CHA_2DS_2-VASc score is 1, the authors recommend OAC or aspirin, with preference toward anticoagulation. If the score is 0, they recom-

Table 2. CHA_2DS_2-VASc Scoring System to Estimate Stroke Risk in Patients With Atrial Fibrillation[20]

Risk Factor	No. of Points
Congestive heart failure or LV dysfunction	1
Hypertension	1
Age $\geq$ 75 yrs	2
Diabetes mellitus	1
Stroke, TIA, or thromboembolism	2
Vascular disease[a]	1
Age 65–74 yrs	1
Sex category (female gender)	1

LV= left ventricular; TIA = transient ischemic attack.
[a]Vascular disease includes prior myocardial infarction, peripheral artery disease, or aortic plaque.

mend aspirin or no antithrombotic therapy at all, with preference toward no antithrombotic therapy. Conversely, the American College of Chest Physicians 2012 antithrombotic therapy for AF guidelines continue to advocate for the use of $CHADS_2$, citing four of five studies that have failed to find a significant improvement in the predictive ability of CHA_2DS_2-VASc over $CHADS_2$.[19] Despite the differences between the guidelines, it may be reasonable to calculate the CHA_2DS_2-VASc score when the $CHADS_2$ score is 0 to ensure that OAC is not withheld in patients who have a substantial risk of thromboembolism when additional known risk factors are considered.

HAS-BLED Scheme to Assess Risk of Bleeding

Whereas the $CHADS_2$ score has been used for many years to assess stroke risk, a convenient schema for determining bleeding risk with antithrombotic therapies has not existed until only recently. The lack of a system for objectively determining bleeding risk has likely contributed significantly to the underuse of OAC in patients with AF, where up to half of patients may be denied therapy with only minimal justification.[22] Although some risk stratification scoring system have been proposed, their use has been limited due to complexity, lack of validation in AF, and significant overlap with stroke stratification schemas.[23–26]

A bleeding stratification schema, termed HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) (Table 3), was developed by incorporating risk factors identified in a derivation cohort and peer-reviewed literature,[27] and its predictive ability in the Euro Heart Survey on AF was studied. The study was composed of 3456 patients for whom the presence or absence of major bleeding at 1-year follow-up was known. Nearly 65% of patients were receiving OAC with a vitamin K antagonist (VKA), 13% were receiving OAC plus aspirin, 24% were receiving either aspirin or clopidogrel, and 10% were not receiving any antithrombotic therapy. In the overall population, the HAS-BLED score was associated with positive predictability (*C* statistic of 0.72), and higher scores were associated with an increased risk of major bleeding.

Based on the results of this study, the investigators advocate for the use of HAS-BLED in conjunction with validated stroke assessment tools to determine the risk versus benefit of OAC. Specifically, they suggest that in high-risk patients ($CHADS_2$ score $\geq$ 2), the risk of bleeding outweighs the benefit of OAC if the HAS-BLED score is greater than the $CHADS_2$ score. If the $CHADS_2$ score is 1, the risk of bleeding outweighs the benefit of OAC if the HAS-BLED score is > 2.

Table 3. HAS-BLED Scoring System to Estimate Bleeding Risk in Patients With Atrial Fibrillation[27]

Risk Factor	No. of Points
Hypertension[a]	1
Abnormal renal and/or liver function (1 point each)	1 or 2
Stroke[b]	1
Bleeding[c]	1
Labile INRs[d]	1
Elderly (> 65 yrs)	1
Drugs predisposing to bleeding and/or excess alcohol use[e] (1 point each)	1 or 2

[a]Hypertension = uncontrolled, systolic blood pressure > 160 mm Hg.
[b]Stroke = previous history of stroke, particularly lacunar.
[c]Bleeding = bleeding history or predisposition (anemia).
[d]Labile INR (international normalized ratio) = therapeutic time in range < 60%.
[e]Drugs predisposing to bleeding or excess alcohol use = antiplatelet agents or nonsteroidal antiinflammatory drug use (1 point) and/or $\geq$ 8 units/wk (1 point).

Although a follow-up study found a higher predictive ability with HAS-BLED compared with other risk stratification tools (*C* statistic of 0.65 vs 0.49–0.64 for other assessment schemas), several concerns remain.[28] First, HAS-BLED significantly overlaps stroke risk assessment tools, as hypertension, age, and stroke are part of both schemas. In addition, it is unclear how valid the HAS-BLED score will be with new oral anticoagulants. For these reasons, the American College of Chest Physicians 2012 antithrombotic therapy for AF guidelines recommend an assessment of bleeding risk when the $CHADS_2$ score is 0–1[19] but do not make specific recommendations regarding which bleeding risk stratification scheme to use. In contrast, European guidelines advocate the use of HAS-BLED in the majority of patients with AF, suggesting a score of 3 or greater indicates high risk and that patients be closely monitored if anticoagulation is initiated.[2]

New Antithrombotic Strategies

For more than 50 years, VKAs have been the mainstay of antithrombotic therapy for patients with AF. However, VKAs present many challenges, including a narrow therapeutic window, frequent monitoring requirements, and significant interpatient and intrapatient variability.[29] In fact, a time in therapeutic range of 55–65% is generally considered acceptable, resulting in patients being

inadequately anticoagulated for up to one-third of the time.[29, 30] Several new anticoagulants, including dabigatran, rivaroxaban, and apixaban, have been developed to mitigate the challenges of VKAs. In addition, dual-antiplatelet therapy with clopidogrel and aspirin has been proposed as an alternative antithrombotic strategy. This review will focus on these new and emerging antithrombotic regimens. A summary of trials is provided in Tables 4[31–34] and 5.[35, 36]

Summary of Clinical Evidence

Dual-Antiplatelet Therapy with Clopidogrel and Aspirin

In the trial of clopidogrel plus aspirin versus oral anticoagulation for AF in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W), 6706 patients with AF were randomized to receive clopidogrel 75 mg plus aspirin 75–100 mg/day or warfarin (goal international normalized ratio [INR] 2.0–3.0). Adjudication of outcomes was blinded, but treatment was open.[34] The trial was terminated after only 1.3 years, when a data and safety monitoring board determined that warfarin was far superior to clopidogrel plus aspirin at reducing the primary composite end point of stroke, systemic embolism, myocardial infarction (MI), or vascular death, a reduction driven primarily by improvements in ischemic stroke and systemic embolism.

The rate of hemorrhagic stroke was lower in the clopidogrel plus aspirin group compared with the warfarin group. However, although there were no significant differences in the incidence of major, severe, or fatal bleeding between the two groups, minor bleeding was significantly lower in the warfarin group (11.45% vs 13.58%/yr, p=0.0009), as was total bleeding (13.21% vs 15.40%/yr, p=0.001).

In a subgroup analysis of stroke severity, warfarin was associated with significantly fewer strokes with no or minor disability (1.40% vs 2.39%/yr, relative risk 2.49, 95% confidence interval [CI] 1.42–4.37), but no significant differences were found in the incidence of moderate, severe, or fatal strokes.

In another subgroup analysis, outcomes appeared to differ based on whether patients were receiving OAC at baseline. In individuals not receiving OAC at study entry, the difference in the primary end point was not significant (4.71% vs 5.89%/yr, p=0.24); however, it was significantly lower in patients randomized to warfarin who were already receiving OAC at study entry (3.72% vs 5.50%/yr, p=0.0005). Major hemorrhage was not significantly different in patients receiving OAC at baseline (clopidogrel plus aspirin 5.89% vs warfarin 4.71%/yr, p=0.11) and not receiving OAC at baseline (clopidogrel plus aspirin 1.73% vs warfarin 2.92%/yr, p=0.09).

In the Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation (ACTIVE A) trial, investigators randomized 7554 patients with AF in whom VKA therapy was deemed unsuitable to receive either clopidogrel 75 mg plus aspirin 75–100 mg/day or aspirin 75–100 mg/day alone.[35] Reasons for not being a suitable candidate for VKA therapy included specific bleeding risks in approximately 25% of patients, physician judgment in 50%, and patient preference in the remaining 25%.

The rate of the primary end point, which was the same as in ACTIVE W, was significantly lower in the clopidogrel plus aspirin arm and was driven primarily by a lower incidence of ischemic stroke. There were no significant differences in rates of hemorrhagic strokes, MI, systemic embolism, or death from vascular causes. More bleeding events were observed in the clopidogrel plus aspirin group (9.7% vs 5.7%/yr, p<0.001), including major, severe, minor, intracranial, and gastrointestinal bleeding, but no significant difference was noted in fatal bleeding (clopidogrel plus aspirin 0.3% vs aspirin 0.2%/yr, p=0.07).

Based on the two ACTIVE studies,[34, 35] it may be reasonable to consider clopidogrel plus aspirin in select patients in whom a VKA is unsuitable. For example, if a patient with AF requires aspirin plus clopidogrel for another indication (e.g., acute coronary syndrome [ACS]) but is unsuitable for triple therapy due to bleeding risks, one may consider clopidogrel plus aspirin as a temporary compromise. In addition, clopidogrel plus aspirin may be considered over aspirin alone in patients who are unsuitable for VKA therapy due to poor compliance or lack of follow-up. However, the combination should not be used in lieu of warfarin in patients with high bleeding risk.[19] The American College of Chest Physicians 2012 antithrombotic therapy for AF guidelines recommend dual-antiplatelet therapy with clopidogrel plus aspirin when OAC is recommended as the treatment of choice but the patient is deemed unsuitable or chooses not to take OAC for concerns other than major bleeding.[19]

Table 4. Summary of Trials Comparing Antithrombotics vs Warfarin in Patients With Nonvalvular Atrial Fibrillation

Variable	RELY[31]	ROCKET AF[32]	ARISTOTLE[33]	ACTIVE W[34]
Intervention	Dabigatran 110 mg b.i.d. or 150 mg b.i.d.	Rivaroxaban 20 mg once/day[a]	Apixaban 5 mg b.i.d.[b]	Clopidogrel 75 mg/day + aspirin 75–100 mg/day
No. of patients	18,113	14,264	18,201	6706
Pertinent exclusion criteria	CrCL < 30 ml/min, active liver disease	CrCL < 30 ml/min, high risk of bleeding, aspirin > 100 mg/day, significant liver disease	Need for aspirin > 165 mg/day, SCr > 2.5 mg/dl, CrCl < 25 ml/min	History of peptic ulcer disease, intracerebral hemorrhage, platelet count < 50×10^3/mm^3
Primary outcome	Stroke and systemic embolism	Stroke and systemic embolism	Stroke and systemic embolism	Stroke, systemic embolism, myocardial infarction, or vascular death
Follow-up period (yrs, median)	2.0	1.9	1.8	1.3
Baseline characteristics				
Age (yrs, median)	71.5	73	70	70
$CHADS_2$ score (mean)	2.1	3.5	2.1	2.0
Efficacy results (event rate [%]/yr; intervention vs warfarin)				
Primary outcome	110 mg: 1.53 vs 1.69 (p<0.001 for noninferiority; p=0.34 for superiority) 150 mg: 1.11 vs 1.69 (p<0.001 for noninferiority; p<0.001 for superiority)	Per protocol[c]: 1.7 vs 2.2 (p<0.001 for noninferiority) Safety, as treated[d]: 1.7 vs 2.2 (p=0.02 for superiority) Intent-to-treat[e]: 2.1 vs 2.4 (p<0.001 for noninferiority; p=0.12 for superiority)	Intent-to-treat: 1.27 vs 1.60 (p=0.01 for superiority)	Intent-to-treat: 5.60 vs 3.93 (p=0.0003 for superiority)
Ischemic stroke	110 mg: 1.34 vs 1.2 (p=0.35) 150 mg: 0.92 vs 1.20 (p=0.03)	1.34 vs 1.42 (p=0.581)	1.19 vs 1.51 (p=0.01)	2.15 vs 1.00 (p<0.0001)
Hemorrhagic stroke	110 mg: 0.12 vs 0.38 (p<0.001) 150 mg: 0.10 vs 0.38 (p<0.001)	0.26 vs 0.44 (p=0.024)	0.24 vs 0.47 (p<0.001)	0.12 vs 0.36 (p=0.036)
INR TTR,% (mean)	64	55	66	64
Safety results (event rate [%]/yr; intervention vs warfarin)				
Major bleeding	110 mg: 2.71 vs 3.36 (p=0.003) 150 mg: 3.11 vs 3.36 (p=0.31)	3.6 vs 3.4 (p=0.58)	2.13 vs 3.09 (p<0.001)	2.42 vs 2.21 (p=0.53)
Intracranial hemorrhage	110 mg: 0.23 vs 0.74 (p<0.001) 150 mg: 0.30 vs 0.74 (p<0.001)	0.5 vs 0.7 (p=0.02)	0.33 vs 0.80 (p<0.001)	0.005 vs 0.003 (p=0.08)
Gastrointestinal bleeding	110 mg: 1.12 vs 1.02 (p=0.43) 150 mg: 1.51 vs 1.02 (p<0.001)	3.2 vs 2.2 (p<0.001)	0.76 vs 0.86 (p=0.37)	Not reported

ACTIVE W = Clopidogrel plus aspirin vs oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; AF = atrial fibrillation; ARISTOTLE = Apixaban vs Warfarin in Patients with Atrial Fibrillation; CrCl = creatinine clearance; RELY = Dabigatran vs Warfarin in Patients with Atrial Fibrillation; ROCKET AF = Rivaroxaban vs Warfarin in Nonvalvular Atrial Fibrillation; SCr = serum creatinine concentration; INR = international normalized ratio; TTR = time in therapeutic range.

[a]Rivaroxaban 15 mg/day was used in patients with CrCl 30–49 ml/min.

[b]Apixaban 2.5 mg b.i.d. was used in patients with ≥ 2 of the following: ≥ 80 yrs old, weight ≤ 60 kg, serum creatinine concentration ≥ 1.5 mg/dl.

[c]ROCKET AF per-protocol population: all patients who received ≥ 1 dose of study drug, did not have a major protocol violation, and were followed for events while receiving a study drug or within 2 days after discontinuation.

[d]ROCKET AF safety, as treated: all patients who received ≥ 1 dose of study drug, regardless of adherence to protocol, and were followed for events while receiving a study drug or within 2 days after discontinuation.

[e]ROCKET AF intent-to-treat - included all patients who underwent randomization and were followed for events during treatment or after premature discontinuation.

Table 5. Trials Comparing Antithrombotics Vs Aspirin in Patients With Nonvalvular Atrial Fibrillation

	ACTIVE A[35]	AVERROES[36]
Intervention	Clopidogrel 75 mg/day + aspirin 75–100 mg	Apixaban 5 mg b.i.d.[a]
No. of patients	7554	5599
Pertinent exclusion criteria	History of peptic ulcer disease in past 6 mo, intracerebral hemorrhage, platelet count < 50 × 10^3/mm^3	Serious bleeding event in previous 6 mo or high risk of bleeding, SCr > 2.5 mg/dl, CrCl < 25 ml/min, significant liver disease
Follow-up period (yrs, median)	3.6	1.1
Primary outcome	Stroke, systemic embolism, myocardial infarction, vascular death	Stroke or systemic embolism
Baseline characteristics		
Age (yrs, median)	71	70
$CHADS_2$ score (mean)	2.0	2.0
Efficacy results (event rate [%]/yr; intervention vs aspirin)		
Primary outcome	6.8 vs 7.6 (p=0.01)	1.6 vs 3.7 (p<0.001)
Ischemic stroke	1.9 vs 2.8 (p<0.001)	1.1 vs 3.0 (p<0.001)
Hemorrhagic stroke	0.23 vs 0.17 (p=NS)	0.2 vs 0.3 (p=0.45)
Safety results (event rate [%]/yr; intervention vs aspirin)		
Major bleeding	2.0 vs 1.3 (p<0.001)	1.4 vs 1.2 (p=0.57)
Intracranial hemorrhage	0.4 vs 0.2 (p=0.006)	0.4 vs 0.4 (p=0.69)
Gastrointestinal bleeding	1.1 vs 0.5 (p<0.001)	0.4 vs 0.4 (p=0.71)

ACTIVE A = Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation; AF = atrial fibrillation; AVERROES = Apixaban in Patients with Atrial Fibrillation; CrCl = creatinine clearance; NS = not statistically significant; SCr = serum creatinine concentration.
[a]Apixaban 2.5 mg b.i.d. was used in patients with ≥ 2 of the following: ≥ 80 yrs old, weight ≤ 60 kg, serum creatinine concentration ≥ 1.5 mg/dl. This dose was used in 6% of patients.

Dabigatran

In the Dabigatran versus Warfarin in Patients with Atrial Fibrillation (RELY) trial, 18,113 patients with AF were randomized to receive the direct thrombin inhibitor dabigatran 150 mg twice/day, dabigatran 110 mg twice/day, or warfarin (goal INR of 2.0–3.0).[31] Dabigatran treatment arms were blinded, whereas warfarin was administered in an unblinded fashion.

For the primary efficacy end point, stroke or systemic embolism, both doses of dabigatran were not inferior to warfarin, but only dabigatran 150 mg was superior. Both dabigatran doses were associated with fewer hemorrhagic strokes than warfarin, but only dabigatran 150 mg was associated with significantly fewer ischemic strokes. More MIs occurred in the dabigatran 150 mg arm compared with warfarin, a difference not observed with the 110-mg dose. The incidence of major bleeding was significantly lower with dabigatran 110 mg, but not with 150 mg, compared with warfarin. Gastrointestinal bleeding was more common with dabigatran 150 mg. Rates of intracranial and minor bleeding were lower with both doses of dabigatran.

The increased risk of MI associated with dabigatran prompted a subsequent review, which identified 28 silent and 4 clinical MIs, demonstrating no significant difference in the annual risk of MI among patients randomized to dabigatran (dabigatran 110 mg 0.82%/yr; dabigatran 150 mg 0.81%/yr; warfarin 0.64%/yr; p=0.09 for dabigatran 110 mg vs warfarin; p=0.12 for dabigatran 150 mg vs warfarin).[37] However, in a recent meta-analysis of dabigatran in patients with AF, ACS, or venous thromboembolism, dabigatran was associated with an increased risk of MI (odds ratio [OR] 1.33, p=0.03).[38] Similar results were observed when the post hoc review of the RELY trial was included and trials of shorter durations were excluded. These results raise the question of whether dabigatran is responsible for increasing MI risk or if the comparator arms have protective effects by comparison. Although a specific mechanism explaining the potential risk of MI with dabigatran has not been elucidated, an unexpected increase (17–31%) in the urinary excretion of 11-dehydrothromboxane B_2, a byproduct of thromboxane A_2 and marker of platelet activation, was observed in the Dabigatran with or without Concomitant Aspirin Compared with Warfarin Alone in Patients with Nonvalvular Atrial Fibrillation (PETRO) trial.[39] Thus, dabigatran could poten-

tially increase the risk of MI by increasing the production of thromboxane A_2.

Another concern with the use of dabigatran is the emerging incidence of adverse events, especially major bleeding, in clinical practice. A QuarterWatch report indicated that dabigatran was responsible for the most numbers of adverse-event reports than any other medication in 2011.[40] In a recent alert issued by the Institute for Safe Medication Practices, dabigatran was responsible for 932 serious adverse events, with approximately 54% of them involving hemorrhage.[41] The median age for patients suffering a hemorrhagic event was 80 years, with 25% being 84 years or older. This raises concern with the use of dabigatran in elderly patients, in whom baseline bleeding risks are higher and estimates of renal function may be inaccurate. In addition, the approved dosage for patients with severe renal impairment (creatinine clearance 15–30 ml/min) is 75 mg twice/day; however, this dosage was not assessed for long-term clinical outcomes but was approved by the FDA largely based on pharmacokinetic studies.[42] It is possible that the lack of long-term studies with the lower dose may also contribute to older patients experiencing postmarketing adverse drug events. Furthermore, it is possible that the increasing bleeding events with dabigatran could be reporting bias given that it is a new medication.

Rivaroxaban

The Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) trial randomized 14,264 patients with AF in a double-blinded manner to the factor Xa inhibitor rivaroxaban 20 mg once/day or warfarin (goal INR 2.0–3.0).[32]

In the intent-to-treat analysis, rivaroxaban was not inferior but not superior to warfarin. In the superiority analysis of the as-treated safety population, the incidence of the primary efficacy end point was significantly lower in the rivaroxaban group compared with warfarin. In addition, 22 patients receiving rivaroxaban experienced a stroke or systemic embolism while discontinuing study drug and/or transitioning to warfarin at the end of the study (vs 7 patients receiving warfarin, p=0.008).[43]

Rivaroxaban was associated with a higher incidence of transfusions (p=0.02) and decreases in hemoglobin of at least 2 g/dl (p=0.04) compared with warfarin, but there were no significant differences in clinically relevant bleeding events or in major bleeding.[32] Conversely, warfarin was associated with higher rates of critical (p=0.007), fatal (p=0.003), and intracranial (p=0.02) bleeding than rivaroxaban.

Several limitations of the ROCKET AF trial have prompted criticism after publication of the study results. First, the INR time in therapeutic range was 55% in the warfarin group compared with rates of 60–65% in other trials. Notably, patients in the ROCKET AF trial were at higher risk, making direct comparisons between trials difficult. Second, patients experienced a greater number of embolic events after discontinuation of rivaroxaban, raising concerns that rivaroxaban may have "rebound" or quick "off" effects. On the other hand, rivaroxaban has the advantage of being the only new OAC to be administered with once-daily dosing; however, some question whether administering rivaroxaban with once-daily dosing is adequate based on its pharmacokinetic properties (i.e., half-life of 5–9 hrs[44]) and whether this may contribute to rebound thromboembolic events.

Apixaban

In the Apixaban in Patients with Atrial Fibrillation (AVERROES) trial, 5599 patients with AF deemed unsuitable for VKA therapy were randomly assigned to the factor Xa inhibitor apixaban 5 mg twice/day or aspirin 81–324 mg once/day.[36] Reasons for unsuitability included labile INR readings (17%), inability to measure INR at appropriate time intervals (43%), $CHADS_2$ score of 1 (21%), and patient preference (38%).

Apixaban was associated with a significant 56% reduction in the occurrence of stroke or systemic embolism compared with aspirin. Rates of ischemic, hemorrhagic, and disabling or fatal stroke were significantly lower in the apixaban arm (p<0.001 for both types of stroke), as were hospitalizations for cardiovascular reasons. No significant differences in hemorrhagic stroke or bleeding were observed.

In the Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) trial, 18,201 patients with AF were randomized in a double-blind fashion to receive apixaban 5 mg twice/day versus warfarin (goal INR of 2.0–3.0).[33]

The rate of stroke or systemic embolism was significantly lower in the apixaban treatment arm compared with warfarin, as were rates of hemorrhagic stroke (apixaban 0.24%/yr vs warfarin 0.47%/yr, p<0.001) and all-cause mortality (apixaban 3.52%/yr vs warfarin 3.94%/yr,

p=0.047). A reduction in major bleeding episodes was also observed in patients receiving apixaban, including a significant reduction in intracranial bleeding. No significant difference was observed in the occurrence of gastrointestinal bleeding.

Whereas all-cause mortality was a secondary end point of ARISTOTLE and should be interpreted with caution, apixaban is the first agent to show a reduction in death, bleeding, and stroke compared with warfarin.

Role in Clinical Practice

Unfortunately, the new anticoagulants have not been compared directly, which complicates clinical decision-making. The American College of Chest Physicians 2012 antithrombotic therapy for AF guidelines recommend dabigatran over warfarin in patients with AF who require OAC based on their $CHADS_2$ score, a recommendation driven largely by the RELY trial results.[19] The nuances of each medication, including safety, efficacy, and the impact of patient-specific characteristics, will emerge with their use in clinical practice. At this time, clinicians should evaluate the impact of patient compliance and secondary end points (e.g., all-cause mortality, incidence of MI and bleeding) and use clinical experience as a guide. In addition, practitioners should consider patient age, kidney function, and bleeding risk. Based on Institute for Safe Medication Practices reports and lack of long-term clinical outcomes data in individuals with a creatinine clearance of less than 30 ml/min, patients who are elderly (> 75 yrs) and/or have poor kidney function may have a more favorable risk-versus-benefit profile with warfarin than with a new OAC, particularly dabigatran. Although similar reports have not yet been observed for rivaroxaban, one should still use caution in older patients with poor kidney function until more practical experience is gained. In patients at higher risk for bleeding, apixaban may represent a safer choice among the new OAC.

One must also consider if a need to transition from warfarin to a new OAC indeed exists. If a patient is well maintained receiving warfarin, does not feel that quality of life is significantly impacted by warfarin use, and has not suffered events related to AF or adverse effects, switching to one of the new agents is unlikely to benefit, particularly when cost is considered. In this case, clinicians should discuss the advantages and disadvantages of each agent and determine which is in the best interest of the patient. Until more evidence emerges from future studies and clinical experience, these decisions should remain individualized.

Cardioversion of AF

Cardioversion of the patient in AF is the preferred acute management strategy when rapid ventricular response is responsible for hemodynamic compromise (e.g., HF, hypotension) or worsening ischemia.[5] Specifically, direct current cardioversion (DCC) is preferred for patients who are hemodynamically unstable.

Cardioversion may be performed by pharmacologic or electrical impulse therapy (DCC).[5] Direct current cardioversion is effective at achieving sinus rhythm but carries the risks incumbent with conscious sedation. Both methods carry a similar risk of stroke in patients who are not fully anticoagulated.

Pharmacologic cardioversion is technically easier to conduct than DCC, but the risks of medication toxicities are of significant concern. It is generally most effective when conducted within 7 days of AF onset, although it is still significantly better than placebo for AF duration of longer than 7 days (or of unknown duration).[5]

Of particular utility in AF of 7 days' duration or less are the Vaughan Williams class IC agents flecainide and propafenone, which can induce cardioversion quickly (within 2–8 hrs for flecainide[45] and 2–6 hrs for propafenone[46]) and effectively (50–90%).[5] These agents may only be used in patients without structural heart disease, limiting their utility in older patients with AF comorbidities such as HF. For patients with known myocardial dysfunction, the class III agents amiodarone and dofetilide are safest and most effective but may require up to 24–30 hours to achieve sinus rhythm.[47, 48] Intravenous ibutilide is also an option for rapid cardioversion (i.e., within 1 hr) but patients must be closely monitored due to the risk of torsade de pointes. As a group, class III agents are more highly recommended over class IC agents for cardioversion of AF that is 7 days or longer in duration.[5]

Given current limitations, the search continues for a fast-acting, highly effective, and safe agent for pharmacologic cardioversion, and vernakalant is the newest agent to be investigated for this indication.

Vernakalant

Vernakalant is a unique antiarrhythmic drug that inhibits both the I_{Na} channel in a voltage- and rate-dependent manner (i.e., most active in a depolarized and fibrillating atrium) and the ultrarapid delayed rectifier current (I_{Kur}), which increases action potential duration and prolongs the atrial refractory period.[49] Because of these effects, vernakalant delays atrial repolarization with little to no impact on ventricular cells, thus limiting the proarrhythmic effects observed with class III agents.

Vernakalant is sequentially metabolized (via demethylation and glucuronidation by cytochrome P450 [CYP] 2D6) to two inactive, renally excreted metabolites.[50] It demonstrates dose-dependent pharmacokinetics and is well distributed into tissues, where its distribution and terminal half-lives are 3–6 minutes and 3 hours, respectively.

Summary of Clinical Evidence

Vernakalant has been studied for the cardioversion of new-onset AF in several clinical phase II and phase III trials (Table 6[51–56]).

In the randomized controlled trial of RSD1235, a novel antiarrhythmic agent, in the treatment of recent-onset atrial fibrillation (Controlled Randomized Atrial Fibrillation Trial [CRAFT]), patients were enrolled into one of three treatment groups of two sequential 10-minute intravenous infusions–vernakalant 2.0 mg/kg followed by 3.0 mg/kg, vernakalant 0.5 mg/kg followed by 1.0 mg/kg, or placebo–separated by 30 minutes.[51] Atrial fibrillation was successfully terminated in 61%, 11%, and 5% of these groups, respectively ($p \leq 0.0005$ for the high-dose group vs placebo), and median time to cardioversion was 11 minutes after the start of the first infusion. No significant QT prolongation or changes in blood pressure were observed. Of note, sinus rhythm was sustained at a greater rate (79% in the high-dose group) at 24 hours compared with placebo (45%).

In the ACT series of trials, vernakalant was administered as 3.0 mg/kg infusion followed by 2.0 mg/kg infusion with a 15-minute observation period in between.[52, 54, 55] In the new-onset AF group, vernakalant cardioverted 51.7% of patients in the Vernakalant Hydrochloride for Rapid Conversion of Atrial Fibrillation (ACT I) trial, 51.2% of patients in the Usefulness of Vernakalant Hydrochloride Injection for Rapid Conversion of Atrial Fibrillation (ACT III) trial, and 51.2% of patients in the Multicenter, Open-Label Study of Vernakalant for the Conversion of Atrial Fibrillation to Sinus Rhythm (ACT IV) trial, compared with approximately 4% in the placebo arms of ACT I and III ($p \leq 0.001$); results were achieved at a mean 8–14 minutes from the start of the first infusion. In the long-duration (lasting 8–45 days) AF group, vernakalant induced cardioversion at a rate of only 7.9–11.6%, compared with 0–2.7% in the placebo groups, a result that was not statistically significant in either ACT I, III, or IV. Sinus rhythm was sustained at a rate of 98% at 24 hours in the vernakalant groups.

The Vernakalant Hydrochloride for the Rapid Conversion of Atrial Fibrillation After Cardiac Surgery (ACT II) trial explored the efficacy of vernakalant after recent cardiac surgery (i.e., coronary artery bypass graft or valve surgery), where the risk for new-onset AF is particularly high.[53] Cardioversion to sinus rhythm was achieved in 44.9% of patients in the vernakalant arm and 14.8% of patients in the placebo arm ($p<0.001$). Of note, in a subgroup analysis, patients randomized to receive vernakalant who were concomitantly treated with rate control therapy (β-blockers, calcium channel blockers, and/or digoxin) achieved cardioversion at a greater rate than did patients who were not (39.4% vs 53.7%, $p=0.0027$). Sinus rhythm was maintained at 24 hours in 60% of the vernakalant-treated patients.

The Randomized Active-Controlled Study Comparing the Efficacy and Safety of Vernakalant to Amiodarone in Recent-Onset Atrial Fibrillation (AVRO) was the first to compare intravenous vernakalant (3.0 mg/kg infusion followed by 2.0 mg/kg infusion) with an active comparator, intravenous amiodarone, and it included more patients with structural heart disease and hypertension than previous trials (~35% and 70%, respectively).[56] Successful cardioversion (defined by achievement of sinus rhythm within 90 min of treatment initiation) was observed in 51.7% of vernakalant-treated patients and 5.2% of amiodarone-treated patients ($p \leq 0.0001$). Sinus rhythm was maintained at 4 hours in 98% of the vernakalant-treated patients.

Vernakalant appears to be a safe alternative to currently available antiarrhythmic drugs. Clinically significant adverse effects involving the cardiovascular system included transient ($\leq$ 90 min) prolongation of the QTc interval (ranging from 0% to 22% greater incidence of Bazett-corrected QT > 500 msec compared with placebo in the trials listed in Table 6) during and

Table 6. Summary of Clinical Trials of Vernakalant for the Cardioversion of AF

Study	Population	Design	Pertinent Exclusion Criteria	Comparators	Primary End Point (Termination of AF at Defined Time Interval)
CRAFT[51] (2004)	AF duration of 3–72 hrs (n=56)	Phase II, MC, DB, RCT	Current hypotension or hypertension, history of QT abnormalities, recent structural heart disease, current use of type I or III V-W agents	Vernakalant 2.0 mg/kg followed by 3.0 mg/kg (group 1) vs vernakalant 0.5 mg followed by 1.0 mg/kg (group 2) vs Pb	Vernakalant group 1 61% vs vernakalant group 2 11% vs Pb 5% ($p \leq 0.0005$ for group 1 vs Pb)
ACT I[52] (2008)	AF duration of 3 hrs–7 days (new-onset group) and 8–45 days (long-duration group) (n=336)	Phase III, MC, DB, RCT	Current hypotension or hypertension, history of QT abnormalities, recent structural heart disease, current use of type I or III V-W agents	Vernakalant 3.0 mg/kg followed by 2.0 mg/kg vs Pb	3 hrs–7 days: vernakalant 51% vs Pb 4% ($p \leq 0.001$) 8–45 days: vernakalant 7.9% vs Pb 0% (p=0.09)
ACT II[53] (2009)	AF or AFl duration of 1–7 days after cardiac surgery (n=161)	Phase III, MC, DB, RCT	Current hypotension or hypertension, history of QT abnormalities, current unstable class IV NYHA HF, current use of type I or III V-W agents	Vernakalant 3.0 mg/kg followed by 2.0 mg/kg vs Pb	Vernakalant 44.9% vs Pb 14.8% ($p \leq 0.001$)
ACT III[54] (2010)	AF or AFl duration of 3 hrs–7 days (new-onset group) and 8–45 days (long-duration group) (n=265)	Phase III, MC, DB, RCT	Current hypotension or hypertension, history of QT abnormalities, recent structural heart disease, current use of type I or III V-W agents	Vernakalant 3.0 mg/kg followed by 2.0 mg/kg vs Pb	3 hrs–7 days: vernakalant 51.2% vs Pb 3.6% ($p \leq 0.0001$) 8–45 days: vernakalant 9.4% vs Pb 2.7% (p=0.330)
ACT IV[55] (2010)	AF duration of 3 hrs–7 days (new-onset group) and 8–45 days (long-duration group) (n=236)	Phase III, MC, open-label.	Current hypotension or hypertension, history of QT abnormalities, recent structural heart disease, current use of type I or III V-W agents	Vernakalant 3.0 mg/kg followed by 2.0 mg/kg (no comparator arm)	3 hrs–7 days: vernakalant 51.2% 8–45 days: vernakalant 11.6%
AVRO[56] (2011)	AF duration of 3–48 hrs (n=254)	Phase III, MC, DB, RCT	Current hypotension or hypertension, history of QT abnormalities, recent structural heart disease, current use of type I or III V-W agents	Vernakalant 3.0 mg/kg followed by 2.0 mg/kg vs amiodarone 5 mg/kg i.v. over 60 min followed by 50 mg over next 60 min	Vernakalant 51.7% vs amiodarone 5.2% ($p \leq 0.0001$)

AF = atrial fibrillation; CRAFT = Controlled Randomized Atrial Fibrillation Trial (randomized controlled trial of RSD1235); MC = multicenter; DB = double-blind; RCT = randomized controlled trial; V-W = Vaughan Williams; Pb = placebo; ACT I = Vernakalant Hydrochloride for Rapid Conversion of Atrial Fibrillation; ACT II = Vernakalant Hydrochloride for the Rapid Conversion of Atrial Fibrillation After Cardiac Surgery; HF = heart failure; NYHA = New York Heart Association; ACT III = Usefulness of Vernakalant Hydrochloride Injection for Rapid Conversion of Atrial Fibrillation; ACT IV = Multicenter, Open-Label Study of Vernakalant for the Conversion of Atrial Fibrillation to Sinus Rhythm; AFl = atrial flutter; AVRO = Randomized Active-Controlled Study Comparing the Efficacy and Safety of Vernakalant to Amiodarone in Recent-Onset Atrial Fibrillation.

shortly after infusion,[52–54, 56] but with no documented instances of on-treatment ($\leq$ 24 hrs after infusion) torsade de pointes. Other adverse effects included bradycardia (in $\leq$ 14% of patients and usually associated temporally with successful cardioversion), hypotension ($\leq$ 6% of patients),[51, 53] and infrequent atrioventricular block.[52, 53] Some patients experienced nonsustained ventricular tachycardia (ranging from 4% in CRAFT to 15% in ACT II), but this was generally at a rate similar to or lower than those in the placebo arms.[51, 52, 54, 55] Notably, conversion to atrial flutter was observed in a subset of patients (5–13% in some trials) but resolved within 4 hours in about 50% of patients.[53, 54, 56] The most common noncardiac adverse effects associated with vernakalant were dysgeusia ($\leq$ 19% of patients), paresthesias (7.4%), and sneezing ($\leq$ 16%).[55]

Role in Clinical Practice

Intravenous vernakalant has been approved for rapid conversion of AF to sinus rhythm in the European Union, Iceland, and Norway, but it is currently undergoing additional phase III studies in the United States.

Vernakalant represents an attractive option for the management of new-onset AF, as it is more effective than placebo, produces cardioversion more quickly than amiodarone,[56] and appears to be less proarrhythmic than ibutilide.[51–56]

Limitations to the use of vernakalant in clinical practice include its lack of efficacy in AF of greater than 72 hours' duration and limited efficacy and safety data in patients with structural heart disease.[52, 54, 55] More patients with AF of greater than 7 days' duration and patients with HF and ACS will need to be studied to determine the utility of vernakalant in these populations.

Maintenance of Normal Sinus Rhythm

Although studies have failed to demonstrate significant advantages with a rhythm control strategy, it is still common in select patient populations.[7–13] Subanalyses of randomized controlled trials indicate a potential benefit with achieving sinus rhythm, attributing the shortcomings to date on the limited efficacy and adverse-effect profiles of available antiarrhythmic drugs.[14, 15] In addition, the growing use of interventional techniques to restore sinus rhythm (which often include adjunct antiarrhythmic drugs) has placed continued emphasis on identifying safe and effective antiarrhythmic drugs.

Given the growing burden of AF worldwide and signals of potential benefit when sinus rhythm can be maintained safely, efforts continue to focus on the search for safe and effective antiarrhythmic drugs. The latest to undergo this process was dronedarone, which has been characterized by less-than-anticipated efficacy outcomes and worsening clinical outcomes in specific patient populations.

Dronedarone

The pharmacology and pharmacokinetics of dronedarone have been discussed in detail previously,[57] so only relevant characteristics will be reviewed here.

The exact mechanism of action of dronedarone is unknown, but, like amiodarone, the agent demonstrates antiarrhythmic properties characteristic of all four Vaughan Williams classes.[57] Dronedarone prolongs the action potential and effective refractory period and exhibits antiadrenergic activity by inhibiting both α- and β-adrenergic receptors. Although it is unknown how these mechanisms contribute to clinical outcomes, dronedarone has been shown to decrease HR and automaticity as well as prolong the QT interval. Some have hypothesized that its effects on adrenergic receptors or inward sodium channels may confer negative inotropic properties, which may be responsible for the worsening outcomes seen with dronedarone in patients with HF.[58, 59]

Notable pharmacokinetic differences between dronedarone and amiodarone include a shorter time to peak and elimination half-life (3–6 and 13–19 hrs, respectively). Due to extensive first-past metabolism in the absence of food, dronedarone should be administered with high-fat meals.[57] Dronedarone is metabolized to both active and inactive metabolites by CYP3A4, making it subject to drug–drug interactions with other enzyme substrates and contributing to its accumulation in patients with hepatic dysfunction. Dronedarone is thought to interact with P-glycoprotein transport, which may be responsible for its effects on serum digoxin concentrations in clinical trials[59, 60]; for this reason, dronedarone may also interact with dabigatran etexilate.

Summary of Clinical Evidence

The safety and efficacy of dronedarone have been evaluated in eight large, randomized controlled trials (Table 7).[58-64]

At a dosage of 400 mg twice/day, dronedarone was effective for the maintenance of sinus rhythm versus placebo.[61, 62] Dronedarone improved the time to AF relapse by a median of 54.7 days versus placebo[61] and reduced the incidence of recurrence at 1 year by 11.1% versus placebo and symptomatic recurrences by 8.3%.[62] However, in a short-term comparison versus amiodarone, dronedarone was less effective in improving the combined end point of AF recurrence or drug discontinuation due to adverse effects or inefficacy (75.1% vs 58.8% with amiodarone), although differences were driven primarily by AF recurrence (42.0% vs 63.5% with amiodarone).[64]

A post hoc analysis of the Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter (EURIDIS and ADONIS) trials found a reduction in hospitalization or death associated with dronedarone compared with placebo in patients with AF (30.9% vs 22.8%, HR 0.73 [95% CI 0.57–0.93], $p<0.01$).[62] This finding was largely responsible for the rationale behind the Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation (ATHENA) trial, where dronedarone reduced a composite end point of cardiovascular hospitalization or all-cause death (31.9% vs 39.4% with placebo) in patients with AF.[63] Contrary to previous investigations of antiarrhythmic drugs, dronedarone appeared to be the first agent to improve cardiovascular mortality and death from cardiac arrhythmias in high-risk patients with AF.

Given the increased incidence of these outcomes in patients with HF, the Increased Mortality After Dronedarone Therapy for Severe Heart Failure (ANDROMEDA) trial evaluated whether dronedarone would confer similar benefits in patients with systolic dysfunction hospitalized due to symptomatic HF (NYHA class III or IV).[58] However, an excess number of deaths in the dronedarone group led investigators to discontinue the study prematurely at 7 months, earning dronedarone a black-box warning in patients with NYHA class IV HF or symptomatic HF (NYHA class II or III) with recent decompensation.[65] Furthermore, the manufacturer of dronedarone (sanofi-aventis, Bridgewater, NJ, USA) was required by the FDA to communicate these risks to health care professionals as part of a risk evaluation and mitigation strategy.[66]

Based on the results of a smaller trial showing an improvement in ventricular rate (reduced by 11.7 bpm vs placebo), dronedarone had also been used for rate control in patients with permanent AF.[60] In the Dronedarone in High-Risk Permanent Atrial Fibrillation (PALLAS) trial,[59] investigators sought to evaluate whether it would confer similar benefits as those observed in ATHENA[63] among the permanent AF population. However, after a median follow-up of only 3.5 months, the study was terminated early due a 2-fold increase in cardiovascular events among patients randomized to dronedarone.[59] The incidence of all-cause mortality, cardiovascular mortality, and arrhythmia-associated mortality was also higher among patients receiving dronedarone, as were strokes, cardiovascular hospitalizations, and hospitalizations for worsening HF. Nearly 70% of patients enrolled in PALLAS had HF; of these, about one-fifth had left ventricular dysfunction, classifying the majority of patients with a history of HF as diastolic in nature. Although previous warnings in patients with HF had been interpreted as applying only to those with systolic dysfunction, the increased rates of morbidity and mortality among patients with diastolic dysfunction in PALLAS may indicate that its use is not safe in this population.

Based largely on the results of PALLAS, the FDA revised the black-box warning for dronedarone, adding that the agent be avoided in patients with permanent AF.[65] In addition, the FDA recommends that providers perform electrocardiograms every 3 months for patients taking dronedarone; if patients are found to be in AF, cardioversion should be attempted or dronedarone discontinued altogether.

Although the rationale behind the development of dronedarone was to identify a safe alternative to amiodarone, the data that have accumulated since its release indicate that dronedarone should only be used in select patients. Data on its adverse effects come from several thousand patients enrolled in clinical trials as well as accounts provided to the FDA, where reports of adverse effects are required as part of a risk evaluation and mitigation strategy program. The most common adverse effects associated with dronedarone are gastrointestinal effects (e.g., diarrhea, nausea, abdominal pain, vomiting), QT prolongation, asthenia, and mild increases (~10%) in serum creatinine concentration unrelated to glomerular filtration rate.[58–64] Severe liver injury has also been reported, including two cases resulting in liver failure and transplantation.[67] Discontinuation due to adverse effects occured in approximately 11.8% of patients treated with dronedarone and 7.7% with placebo.[65] Compared with amiodarone, overall adverse effects are similar with dronedarone.

Table 7. Summary of Clinical Trials of Dronedarone in Patients with AF

Trial	Study Objective	Pertinent Inclusion and Exclusion Criteria	Dronedarone Regimen	No. of Patients	Study Duration	Efficacy Outcomes	Safety Outcomes
DAFNE[61]	Maintenance of normal sinus rhythm in AF	Inclusions: persistent AF scheduled for cardioversion Exclusions: recent cardioversions or CV events, high-risk ECG abnormalities (e.g., QT prolongation, history of torsade de pointes, severe bradycardia, atrioventricular block), NYHA class III–IV HF, LVEF < 35%	400 mg, 600 mg, or 800 mg b.i.d. vs placebo	199	≤ 6 mo	Extended time to AF recurrence, 60 days vs 5.3 with placebo (RRR 0.55, 95% CI 28–72%, p=0.001)	Greater GI adverse effects (4.4% vs 0% with placebo) Greater discontinuations due to adverse events (10.8% vs 0% with placebo)
EURIDIS and ADONIS[62]	Maintenance of normal sinus rhythm in AF	Inclusions: AF in normal sinus rhythm for ≥ 1 hr Exclusions: permanent AF, high-risk ECG abnormalities, NYHA class III–IV HF, renal impairment	400 mg b.i.d. vs placebo	1237	12 mo	Decreased AF recurrence at 12 mo (64.1% vs 75.2% with placebo) (HR 0.75, 95% CI 0.65–0.87, p<0.001) Decreased symptomatic recurrences (37.7% vs 46.0% with placebo) (p<0.001)	Greater serum creatinine concentration elevations (2.4% vs 0.2% with placebo) (p=0.004) Greater discontinuations due to adverse effects (148 vs 60 with placebo)
ERATO[60]	Impact on ventricular rate in AF	Inclusions: permanent AF with resting ventricular rate ≥ 80 bpm Exclusions: unstable angina, high-risk ECG abnormalities, NYHA class III-IV HF	400 mg b.i.d. vs placebo	174	6 mo	Decreased 24-hr ventricular rate by a mean of 11.7 bpm vs placebo (p<0.001) and rate during maximal exercise by 27.4 bpm (vs 2.9 bpm with placebo) (p<0.001); decreased rate during submaximal exercise by 27.4 bpm (vs 2.2 bpm with placebo) (p<0.0001)	Higher rate of overall adverse effects vs placebo (77% vs 60%) Higher rate of GI adverse events vs placebo Greater impact on digoxin serum concentrations vs placebo

(continued)

Table 7. (continued)

Trial	Study Objective	Pertinent Inclusion and Exclusion Criteria	Dronedarone Regimen	No. of Patients	Study Duration	Efficacy Outcomes	Safety Outcomes
ANDROMEDA[58]	Effect on mortality and hospitalizations in HF	Inclusions: hospitalization with new or worsening NYHA class III–IV HF, LVEF $\leq$ 35% Exclusions: recent MI, high-risk ECG abnormalities, planned or recent surgery, other significant structural cardiac disease	400 mg b.i.d. vs placebo	627	7 mo (trial was stopped early)	Primary composite end point of all-cause mortality or hospitalization for HF was not significantly different between the two groups, but the trial was terminated early due to increased mortality with dronedarone (8.1% vs 3.8% with placebo) (HR 2.12, 95% CI 1.07–4.25, p=0.03); dronedarone exposure was also a predictor of mortality (HR 2.19, 95% CI 1.06–4.52, p=0.03); hospitalizations for CV causes also higher with dronedarone (71 patients vs 50 with placebo, p=0.02)	Excluding events resulting in death, an increase in serum creatinine concentration was the only other significant difference between the groups (8 patients with dronedarone vs 0 with placebo)
ATHENA[63]	Hospitalization due to CV causes or death in high-risk patients with AF	Inclusions: paroxysmal or persistent AF or AFl and age > 75 yrs, or age 71–74 yrs and $\geq$ 1 high-risk feature (e.g., hypertension, diabetes mellitus, previous stroke or systemic embolism, LVEF $\leq$ 40%) Exclusions: permanent AF, unstable hemodynamics, AMI, high-risk ECG abnormalities, severe renal impairment	400 mg b.i.d. vs placebo	4628	22 mo (median)	Decreased the primary composite end point of CV hospitalization or all-cause death (31.9% vs 39.4% with placebo) (HR 0.74, 95% CI 0.67–0.82, p<0.001); also decreased CV death (2.7% vs 3.9% with placebo) (HR 0.71, 95% CI 0.51–0.98, p=0.03), hospitalizations due to atrial fibrillation (14.6% vs 21% with placebo, p<0.001), acute coronary syndromes (2.7% vs 3.8% with placebo, p=0.03), and death from cardiac arrhythmias (1.1% vs 2.1% with placebo, p=0.01)	Discontinuations were similar between the two groups, although more patients randomized to dronedarone discontinued therapy due to adverse effects (12.7% vs 8.1% with placebo)

(continued)

Table 7. (continued)

Trial	Study Objective	Pertinent Inclusion and Exclusion Criteria	Dronedarone Regimen	No. of Patients	Study Duration	Efficacy Outcomes	Safety Outcomes
DIONYSOS[64]	Efficacy and safety vs amiodarone in AF	Inclusions: persistent AF Exclusions: contraindication to amiodarone, thyroid disease, high-risk ECG abnormalities, NYHA class III–IV HF	400 mg b.i.d. vs amiodarone 600 mg/day for 28 days, then 200 mg/day	504	7 mo (median)	Inferior to amiodarone for the combined efficacy and safety end point (time to recurrence or drug discontinuation due to inefficacy or adverse effects) (75.1% vs 58.8% with amiodarone) (HR 1.59, 95% CI 1.28–1.98, p<0.0001), which was primarily driven by discontinuation due to inefficacy with dronedarone (42.0% vs 63.5% with amiodarone)	No significant difference in the combined safety end point (39.3% vs 44.5% with amiodarone) (HR 0.80, 95% CI 0.60–1.07, p=0.129); when GI events were excluded, safety end points favored dronedarone (HR 0.61, 95% CI 0.44–0.84, p=0.002); patients randomized to amiodarone had higher rates of thyroid and neurologic events as well as supratherapeutic INRs and hemorrhagic events (11.3% vs 5.6% with dronedarone) (p=0.03)

(continued)

Table 7. (continued)

Trial	Study Objective	Pertinent Inclusion and Exclusion Criteria	Dronedarone Regimen	No. of Patients	Study Duration	Efficacy Outcomes	Safety Outcomes
PALLAS[59]	Major vascular events or unplanned CV hospitalization in permanent AF	Inclusions: permanent AF or AFl and age > 65 yrs with $\geq$ 1 high-risk feature (e.g., CAD, previous stroke or TIA, NYHA class II-III HF, LVEF < 40%, PAD); or age $\geq$ 75 yrs with hypertension and diabetes mellitus Exclusions: paroxysmal or persistent AF, implantable AICD, high-risk ECG abnormalities	400 mg b.i.d. vs placebo	3236	3.5 mo (median) (trial was stopped early)	Associated with increased occurrence of the primary composite end point of stroke, MI, systemic embolism, or death from CV causes (43 patients vs 19 with placebo) (HR 2.29, 95% CI 1.34–3.94, p=0.002) when the trial was terminated early; dronedarone also increased the rate of unplanned CV hospitalization or death (127 patients vs 67 with placebo) (HR 1.95, 95% CI 1.45–2.62, p<0.001); rates of all-cause mortality, CV mortality, arrhythmia-related mortality, stroke, CV hospitalization, and hospitalization for worsening HF were higher in the dronedarone group	Aside from those related to efficacy outcomes, dronedarone was also associated with increased alanine aminotransferase levels > 3 times the upper limit of normal (1.5% vs 0.5% with placebo) (p=0.02)

AF = atrial fibrillation; DAFNE = Dronedarone Atrial FibrillatioN study after Electrical Cardioversion; GI = gastrointestinal; CV = cardiovascular; ECG = electrocardiogram; RRR = relative risk reduction; CI = confidence interval; NYHA = New York Heart Association; HF = heart failure; LVEF = left ventricular ejection fraction; EURIDIS and ADONIS = Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter; ERATO = Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation; bpm = beats/minute; ANDROMEDA = Increased Mortality After Dronedarone Therapy for Severe Heart Failure; MI = myocardial infarction; ATHENA = Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation; CV = cardiovascular; AFl = atrial flutter; AMI = acute myocardial infarciton; HR = hazard ratio; DIONYSOS = Short-term, Randomized, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation; AMI = acute myocardial infarction; INR = international normalized ratio; PALLAS = Dronedarone in High-Risk Permanent Atrial Fibrillation; CAD = coronary artery disease; TIA = transient ischemic attack; PAD = peripheral arterial disease; AICD = automated implantable cardioverter-defibrillator.

However, when gastrointestinal events are excluded, adverse effects are fewer with dronedarone (HR 0.61, 95% CI 0.44–0.84, p=0.002) and tend to be less severe (e.g., fewer thyroid and neurologic complications).[64] Based on these and other findings, dronedarone is contraindicated in patients with NYHA class IV HF or symptomatic HF (NYHA class II-III), high-degree atrioventricular block or sick sinus syndrome (in the absence of a pacemaker), severe bradycardia, QTc interval of 500 msec or greater or concomitant drugs known to prolong the QT interval, concomitant use of strong CYP3A4 inhibitors, and severe hepatic impairment or history of hepatic dysfunction related to the use of amiodarone and in women who are pregnant or nursing.[65]

Several clinically important drug interactions have also been observed with dronedarone, including interactions with digoxin, VKAs, dabigatran, and simvastatin. In the PALLAS trial, patients receiving dronedarone had an elevated mean serum digoxin concentration (1.2 ± 0.8 ng/ml) versus placebo (0.9 ± 0.6 ng/ml).[59] In addition, the mean time in therapeutic range for patients receiving VKAs (INR 2–3) was less in the dronedarone group (55.6%) compared with the placebo group (58.6%, p=0.02); however, the authors did not think that this difference was significant enough to account for the increased risk of stroke observed in the trial. In the Short-term, Randomized, Double-Blind, Parallel-Group Study to Evaluate the Efficacy and Safety of Dronedarone versus Amiodarone in Patients with Persistent Atrial Fibrillation (DIONYSOS) trial, interactions between dronedarone and warfarin were less severe than those between amiodarone and warfarin based on differences in supratherapeutic INR values and hemorrhagic events (11.3% in the amiodarone group vs 5.6% in the dronedarone group, p=0.03).[64] In patients with moderate renal impairment (i.e., creatinine clearance 30–50 ml/min) who are taking dronedarone, the recommended dosage of dabigatran is 75 mg twice/day.[42] Furthermore, in patients taking dronedarone, the dosage of simvastatin should not exceed 10 mg/day.[65]

Role in Clinical Practice

In summary, dronedarone remains an option in patients without overt structural heart disease and in whom amiodarone should be avoided. Although it is less effective than amiodarone at maintaining sinus rhythm and only marginally effective compared with placebo, it remains indicated for reducing the risk of hospitalization in patients with a history of AF but in whom sinus rhythm has already been restored. Dronedarone should be used with caution in patients with structural heart disease, given evidence of worsening outcomes in patients with both systolic and diastolic dysfunction HF as well as other forms of cardiovascular disease. Furthermore, the latest recommendations by the FDA to perform frequent monitoring of liver function (periodically, especially during the first 6 mo of treatment) and electrocradiograms make it a less convenient alternative for many providers.

Dronedarone has been incorporated into recent practice guidelines promulgated by authorities in the United States and Europe.[2, 17] Similar to other antiarrhythmic drugs, its use requires appropriate patient selection based on the presence or absence of structural heart disease. Some notable differences exist between the U.S. and European guidelines. In the 2010 European Society of Cardiology guidelines, dronedarone may be considered before amiodarone in patients without heart disease as well as those with left ventricular hypertrophy, coronary artery disease, and stable NYHA class I-II HF.[2] However, recommendations for the use of dronedarone are more conservative in the U.S. guidelines, where it is not recommended in patients with substantial left ventricular hypertrophy or any class of HF.[17] Dronedarone is also recommended as a first-line option in patients with minimal or no structural heart disease and in those with coronary artery disease.

Although ongoing research with dronedarone appears to be mostly concluded, interest in its use may be renewed with the Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation (HARMONY) trial,[68] which pairs a lower dose of dronedarone with ranolazine, an antianginal drug with sodium channel–inhibiting properties and some evidence of benefit in a variety of arrhythmias.[69–71] Given evidence from animal models that the two drugs may have synergistic antiarrhythmic effects in atrial tissue, the HARMONY trial will randomize patients with paroxysmal AF to dronedarone, ranolazine, or a fixed-dose combination of the two drugs. In the meantime, it is unlikely that the use of dronedarone will expand significantly given its overall lack of efficacy and growing safety concerns.

Catheter Ablation

Despite the use of antiarrhythmic drug therapy, patients may remain symptomatic from recurrent AF. As a result, catheter ablation has emerged as a strategy for eliminating the underlying electrophysiologic causes of AF. Arrhythmogenesis in AF commonly results from both a trigger (i.e., ectopic beats originating from the pulmonary vein) and a substrate for perpetuating an aberrant impulse (i.e., junction of the pulmonary vein and left atria). In catheter ablation, the trigger and substrate are dissociated by radiofrequency energy or freezing (cryoablation), thereby eliminating electrical conduction from the pulmonary vein to the left atria. Currently, both radiofrequency ablation and cryoablation are FDA approved for the management of paroxysmal AF. These techniques are also used to manage persistent or permanent AF but are not yet approved by the FDA.[2, 72] Current guidelines recommend the use of catheter ablation as an alternative to antiarrhythmic drug therapy in patients with symptomatic AF and little or no left atrial enlargement.[5]

To date, there are no published studies evaluating the effect of catheter ablation versus antiarrhythmic drugs on major clinical outcomes. Preliminary results from the second Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Therapy of Atrial Fibrillation (RAAFT-2) trial indicate that catheter ablation may be more effective than antiarrhythmic drugs in reducing AF recurrence when used as first-line therapy.[73] The ongoing Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) study compares left atrial catheter ablation to either rate control or rhythm control drugs in reducing total mortality in patients with untreated or incompletely treated AF.[74] Currently, literature supporting the use of catheter ablation therapy compares this strategy to antiarrhythmic drugs in patients with paroxysmal AF who have already failed one antiarrhythmic drug. Meta-analyses have been published on the use of catheter ablation in select populations of patients with AF.[75, 76] One meta-analysis of six trials comparing standard medical management with catheter ablation found that catheter ablation significantly increased freedom from AF (OR 9.74, 95% CI 3.98–23.87).[76] One important limitation of the studies performed to date is that they were conducted at centers with expertise in catheter ablation therapy; replicating these successes assumes that an experienced practitioner is performing the procedure.[73, 75, 76]

Trials evaluating catheter ablation for AF include a "blanking period," or a period immediately following catheter ablation where AF recurrence is not considered treatment failure. As the left atrium heals from scars made during the procedure, patients may move between sinus rhythm and AF.[2, 72] During this period, clinicians may use antiarrhythmic drug therapy to promote sinus rhythm, a practice that is accepted in the literature evaluating catheter ablation.[75, 76] Blanking periods in clinical trials range from 1 to 3 months, with most trials favoring a 3-month duration. In clinical practice, many practitioners evaluate antiarrhythmic drug use at the end of the blanking period to determine whether continuation would confer additional benefit in individual patients. Analyses from clinical trials evaluating the success of catheter ablation support that more patients remain free of AF when catheter ablation and antiarrhythmic drug therapy are used in combination for long-term management.[77]

Because patients may experience recurrent AF for 1–3 months after catheter ablation, OAC must be continued during this time even if the procedure is successful. The 2010 European Society of Cardiology guidelines outline specific recommendations for anticoagulation after catheter ablation, suggesting that patients be bridged with unfractionated heparin or low-molecular-weight heparin to OAC.[2] The recommended duration of OAC is a minimum of 3 months (i.e., matching the length of the blanking period); thereafter, patients should be evaluated for ongoing OAC based on the presence or absence of AF and the relative risk of stroke based on accepted scoring schemes. Similarly, the American College of Chest Physicians 2012 antithrombotic therapy for AF guidelines recommend making antithrombotic therapy decisions based on the $CHADS_2$ score, regardless of the underlying rhythm.[19] If the decision to continue OAC is made, patients should be counseled on the importance of long-term therapy despite successful ablation.

Upstream Therapy

Upstream therapy refers to the use of nonantiarrhythmic drugs that alter the atrial substrate or target specific mechanisms of AF to provide primary prevention of new-onset AF or secondary prevention of recurrent AF. These therapies target fibrosis, hypertrophy, inflammation, and oxidative stress, as well as other alterations associated

with atrial remodeling known to occur with aging and progressive heart disease.[78–80]

Although randomized controlled trials for primary prevention of AF have not been conducted, retrospective studies have demonstrated a reduction in new-onset AF with some agents. Specifically, new-onset AF was reduced with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in patients with significant underlying heart disease, and new-onset AF after cardiac surgery was reduced with statin therapy.[79] Less compelling data exist for the role of upstream therapies in the secondary prevention of AF. Whereas some small studies and retrospective analyses suggested a benefit in secondary prevention, larger randomized controlled trials have demonstrated equivocal or negative outcomes.[80] Regarding the role of upstream therapy in reducing mortality and major nonfatal cardiovascular events in primary or secondary prevention of AF, additional studies are needed.

Primary Prevention

Inhibitors of the Renin-Angiotensin-Aldosterone System

Angiotensin II stimulates atrial fibrosis and hypertrophy resulting in arrhythmogenesis, whereas aldosterone stimulates inflammation, hypertrophy, and fibrosis and likely has direct electrophysiologic effects, making the renin-angiotensin-aldosterone system (RAAS) a potential target for upstream therapy.[81, 82] Retrospective analyses of multiple large trials in patients with HF have demonstrated a reduced occurrence of new-onset AF with several ACE inhibitors.[83–85] Four meta-analyses demonstrated reduced risk of new-onset AF (30–48%) in patients with HF.[86–89] In hypertension, only one of four meta-analyses found a beneficial effect of ACE inhibitors and ARBs on the prevention of incident AF. Similarly, the effects are less well defined in patients with multiple cardiovascular risk factors.[90, 91] Retrospective studies have failed to demonstrate a significant beneficial effect of RAAS inhibition on occurrence of AF after cardiac surgery.[92–95] Studies assessing the role of aldosterone antagonists on new-onset AF have primarily been conducted in animals. Overall, new-onset AF is reduced in patients with significant underlying heart disease (e.g., left ventricular dysfunction and hypertrophy) treated with ACE inhibitors or ARBs, but evidence is much less robust in patients with individual or multiple cardiovascular risk factors such as hypertension and diabetes mellitus.[81, 82]

Statins

The precise mechanism for the benefit of statins in the primary prevention of AF remains unclear; however, it is hypothesized to be multifactorial and includes antihyperlipidemic and subsequent antiatherosclerotic effects, as well as effects on inflammation, oxidation, endothelial function, and neurohormonal activity, among other potential effects.[96] In patients with HF, several retrospective analyses from randomized controlled trials and registries have demonstrated a modest reduction (13–31%) in the incidence of AF with the use of statins.[97–101] In hypertensive patients, very limited evidence exists to support the role of statins in primary prevention of AF.[102–104] In patients with coronary artery disease, several small observational or post hoc analyses suggest a reduction in new-onset AF with statin therapy; however, a large Veterans Affairs database of patients with coronary artery disease found no benefit.[105] A series of studies in patients with ACS is equally debatable. These studies have a variety of limitations, including retrospective design, small sample size, and short duration of follow-up.[106, 107] In patients with prior stroke or transient ischemic attack, high-dose atorvastatin did not reduce the incidence of new-onset AF.[108] A systematic review (three randomized clinical trials and 10 observational studies with a total of 17,643 patients) and meta-analysis (eight randomized clinical trials with a total of 743 patients) have suggested a reduced incidence of postoperative AF of 23% and 43%, respectively, with the use of statins.[109, 110] Overall, the role of statins in primary prevention of AF has not been sufficiently demonstrated, with the exception of benefit in patients undergoing cardiac surgery.

Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (n-3 PUFAs) have been hypothesized to prevent new-onset AF through a variety of mechanisms, including antiarrhythmic, antiinflammatory, and antioxidant effects.[111] Only one of five epidemiologic studies of n-3 PUFAs demonstrated benefit in the prevention of AF.[112] The majority of these five epidemiological studies are limited, and the benefit was only noted with broiled or baked fish consumed 1–4 times a

week compared with fish consumed less than once a week. A database of patients hospitalized for MI demonstrated fewer hospitalizations for AF at 1 year in patients prescribed n-3 PUFAs.[113] In patients with postoperative AF, many small studies have been conducted with varying results. Thus, the literature documenting the role of n-3 PUFAs for the primary prevention of AF is inadequate.

Secondary Prevention

Given the limited and controversial experimental and clinical data on secondary prevention of AF, no strong recommendation can be made regarding the use of upstream therapies for the reduction of AF recurrences. Several ongoing trials are set to investigate the antiarrhythmic effect of various agents for the secondary prevention of AF.[78, 80]

Conclusion

Although substantial advances in the treatment of AF have been made over the past decade, significant uncertainty surrounds optimal management of this condition. Atrial fibrillation continues to be an area of ongoing research, as it remains a significant burden to individual patients and to society as a whole. Given the rapid evolution of literature in this therapeutic area, we hope this review emphasizes not only the recent developments in the management of AF but also the importance of clinicians staying up-to-date on the literature surrounding this condition.

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