Acute Management of Atrial Fibrillation*

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Acute atrial fibrillation (AF) is the most common cardiac rhythm encountered in clinical practice and is commonly seen in acutely ill patients in critical care. In the latter setting, AF may have two main clinical sequelae: (1) haemodynamic instability and (2) thromboembolism. The approach to the management of AF can broadly be divided into a rate control strategy or a rhythm control strategy, and is largely driven by symptom assessment and functional status. A crucial part of AF management requires the appropriate use of thromboprophylaxis. In patients who are haemodynamically unstable with AF, urgent direct current cardioversion should be considered. Apart from electrical cardioversion, drugs are commonly used, and Class I (flecainide, propafenone) and Class III (amiodarone) antiarrhythmic drugs are more likely to revert AF to sinus rhythm. Beta blockers and rate limiting calcium blockers, as well as digoxin, are often used in controlling heart rate in patients with acute onset AF. The aim of this review article is to provide an overview of the management of AF in the critical care setting.
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Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by rapid, irregular, and chaotic atrial activity with consequent deterioration of atrial mechanical function.[1] Given that AF is commonly associated with many cardiac and noncardiac conditions, including acute illnesses, it is not surprising that AF is commonly seen in the critical care setting. After all, AF is the most common sustained tachyarrhythmia with an incidence of around 5% in those > 65 years of age rising to around 10% in the population > 80 years.[2]

In the critical care setting, clinicians would commonly encounter so-called acute AF, and this terminology includes AF of < 48 h duration and includes both paroxysmal AF (with a paroxysm occurring in the critical care setting, consequent on—or causing—the acute illness) or the first symptomatic presentation of persistent AF.[3]

How common is this problem? The epidemiology of acute AF is less well defined, but among acute emergency admissions in two UK-based prospective surveys, around 3 to 6% of patients had AF,[4,5] of which 34% were of new onset.[5] This compares to a prospective survey conducted in New Zealand, which estimated the prevalence of acute AF in emergency admissions to be around 10%.[6] Only a few data are available regarding the incidence and type of arrhythmias in critically ill patients. For example, one study reviewed 310 arrhythmia episodes in 133 patients in ICUs and found that up to 30% of the reported arrhythmias were AF.[7] It is assumed that the use of inotropes and other vasoactive agents contributes to new-onset AF. Furthermore, prolonged immobilization (leading to pulmonary embolism), infections, and so on, could be other predisposing factors.

The development of AF in the critical care setting may have two main clinical sequelae: (1) hemody-

namic, leading to hypotension, heart failure, and so on, and (2) thromboembolic, resulting in stroke and systemic thromboembolism. In the postoperative setting, AF is common, occurring in up to 50% of postcardiac surgery subjects, leading to prolonged hospital stays and greater health-care costs.[8] The development of a stroke associated with acute AF leads to a high mortality, but in survivors of AF-related stroke, the risk of recurrence is high, and such patients have a greater disability and lower rate of discharge to their own homes.[8] In the context of acute myocardial infarction, AF leads to an increased risk ratio for total mortality, of 1.33 (95% confidence interval [CI], 1.19 to 1.49; p < 0.0001).[9]

This review article provides an overview of the management of AF in the critical care setting.

Search Strategy

We did a comprehensive literature search by using electronic databases in Medline and PubMed. Relevant articles were selected for inclusion, and reference lists from included articles were scanned for additional literature. Keywords for searching including *acute atrial fibrillation, cardioversion, rate control,* and *anticoagulation.*

Clinical Presentation

Around 50% of patients presenting with acute AF revert spontaneously back to sinus rhythm within 48 h.[3] Furthermore, this is more likely to occur if an underlying etiology is identified and treated. However, there is no available evidence to quantify precisely the proportion of patients who progress to develop chronic AF.

AF may present as a consequence of its symptoms (palpitations, breathlessness, dizziness, and chest pain), hemodynamic consequences (syncope), or embolic complications, notably ischemic stroke.[10,11]

The onset of acute AF is associated with a reduction in cardiac output by up to 20% and can lead to the development of heart failure,[12] which carries a worse prognosis. Patients in AF lack the normal atrial systolic function and the contribution to diastolic ventricular filling, thus reducing the overall stroke volume. AF also causes changes on the myocardium and progressive dilatation of the left atrium. Poorly controlled AF rates results in ventricular dilatation and impaired systolic function, the so-called tachycardia-induced cardiomyopathy.[13] The effect of reduced stroke volume and cardiac output is more profound in patient with structural heart disease.

Acute AF is associated with a risk of ischemic stroke.[14,15] Importantly, there is a clustering of strokes particularly at the time of onset of AF.[16]

Indeed, atrial thrombi are even present on transesophageal echocardiography in 15% of patients with AF of < 48 h duration[17] However, this may reflect that the fact that many patients develop AF asymptomatically and only present acutely after decompensation and/or the development of symptoms.

Treatment of Acute Atrial Fibrillation

Once identified, the assessment of acute AF involves making a full clinical assessment, confirming the diagnosis of AF with a surface 12-lead ECG and treating any reversible etiology. In particular, etiologies such as Wolff-Parkinson-White syndrome need attention because atrioventricular node blocking therapies are contraindicated.[18]

In the acute AF setting, the debate of rate vs rhythm control, anticoagulation, and performing specialist investigation such as transthoracic echocardiography are counterbalanced by the urgency to initiate treatment,[19] and such decisions hinge on the clinical status of the patient. Figure 1 shows a schematic representation of the management of acute AF.

Patients With Hemodynamic Instability: The initial assessment of patients with acute AF involves the identification of critically unwell patients. The evidence-based UK National Institute for Health and Clinical Excellence (NICE),[11] the joint American-European AF guidelines,[1] and the European Resuscitation Council Guidelines[20] recognize such pa-
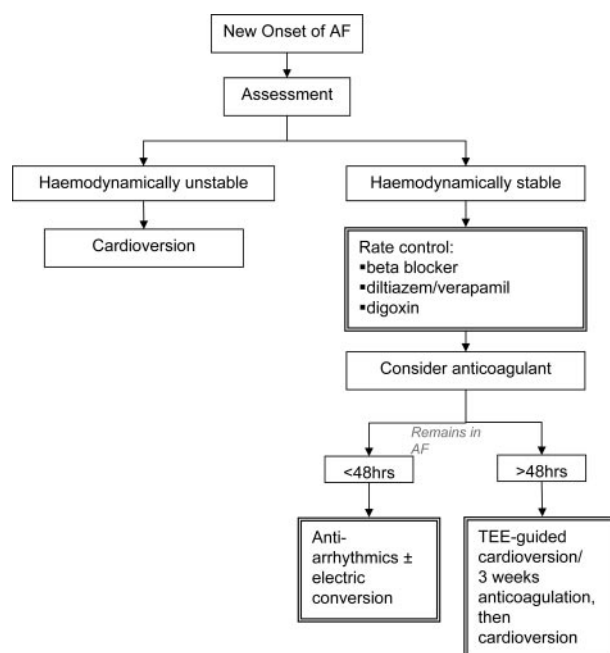

FIGURE 1. The management of acute AF. TEE = transesophageal echocardiography.

tients as those with ventricular rates > 150, ongoing chest pain, or with evidence of critical perfusion: systolic BP < 90 mm Hg, heart failure, or reduced consciousness.

The need to restore hemodynamic stability by the restoration of sinus rhythm is of prime importance, and guideline consensus advocates direct current cardioversion (DCC) as first-line therapy to achieve this, with pharmacologic strategies being used either second or in conjunction with DCC. However, there is no clinical evidence for this management strategy because it would be unethical to conduct randomized controlled trials in such acutely unstable patients. Figure 2 summarizes the approach to managing such patients.

As for DCC, no evidence is available to help guide decisions regarding anticoagulation in acute hemodynamically unstable AF. Consensus guidelines advocate the administration of heparin before cardioversion, and whether this is continued after DCC is based on the patient's intrinsic risk of thromboembolism.[1] There is no significant difference on whether low molecular weight heparin or unfractionated heparin is used before cardioversion (see later). Oral anticoagulation with warfarin is not recommended in acute AF before cardioversion due to its slow onset of action.

Patients With Hemodynamic Stability: With patients presenting with stable acute AF, the decisions regarding its management are relatively less urgent,

and treatment should be directed to symptom relief and the prevention of complications while taking into consideration any coexisting comorbidities and etiologies.

Pharmacotherapy involves decisions relating to rate control, rhythm control, and anticoagulation. Such antiarrhythmic drugs (AADs) can be classified by the Vaughan Williams classification system (Table 1). Table 2 summarizes the AADs that are available in the acute setting.

Generally class I and III agents are used when adopting a rhythm-controlling strategy, whereas class II and IV agents are reserved for rate-controlling measures, although class III agents share rate-controlling properties. This section reviews the commonly used drugs—class Ic (flecainide, propafenone), class II (β-blockers), class III (amiodarone), class IV (diltiazem, verapamil, and digoxin)—in the management of acute AF.

Class IC Agents

Flecainide: A number of randomized controlled trials (RCTs)[21–24] have compared the efficacy of flecainide in converting AF to sinus rhythm compared to placebo and/or other AADs (Table 3). Flecainide is effective in converting atrial fibrillation to sinus rhythm compared with placebo. Conversion time is shorter for flecainide compared with amiodarone.

Despite the evidence supporting the effectiveness of flecainide for the cardioversion of acute AF, it must be emphasized that patients with coronary artery disease, cardiomyopathy, and hemodynamic instability were excluded from the trials. With the evidence of increased mortality from the Cardiac Arrhythmia Suppression Trial (CAST) study, flecainide with its increased proarrhythmia risk is contraindicated in patients with a history of acute coronary ischemia.[25] Furthermore, its use is contraindicated in patients with structural heart disease or cardiomyopathy and hemodynamic instability due to the risk of cardiac decompensation.[11]

Propafenone: There have been a number of RCTs and a systematic review investigating the effectiveness of propafenone in the cardioversion of AF.

The systematic review conducted by Reimold et al[26] reviewed flecainide in patients with supraventricular tachycardia (n = 1,843) and propafenone was found to be successful in 83.8% of patients (95% CI, 78.1 to 89.7). However, patients with both acute and chronic AF were included in the systematic review. In the trials that included propafenone, this was given either IV (2 mg/kg bolus followed by infusion) or orally (450 to 600 mg). Furthermore, the likelihood of converting a paroxysm of AF increased over time of therapy, with
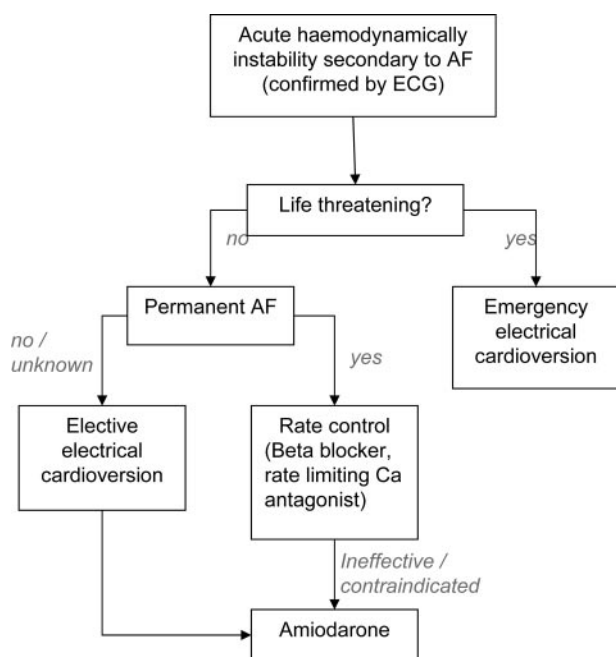

FIGURE 2. The management of AF with hemodynamically instability.

Table 1—Vaughan Williams Classification of AADs*

Class	Action	Drugs	Cautions
Ia	Sodium channel inhibition: prolong repolarization	Quinidine, procainamide, disopyramide	History of myocardial infarction, congestive heart failure, renal disease
Ib	Sodium channel inhibition: shorten repolarization	Lidocaine	Proarrhythmias
Ic	Sodium channel inhibition: no effect on repolarization but reduce conductivity	Flecainide, propafenone	Structural heart disease, history of myocardial infarction, congestive heart failure
II	β-Adrenergic inhibition	Timolol, esmolol, atenolol, bisoprolol	Acute heart failure, bronchospasm
III	Potassium channel inhibition: prolong repolarization	Amiodarone, sotalol†	Renal disease, pulmonary disease
IV	Calcium channel inhibition	Verapamil, diltiazem	Not in conjunction with β-blockers
Miscellaneous	Na-K ATPase inhibition: potentiate parasympathetic response	Digoxin	Renal disease, hypokalemia

*ATPase = adenosine triphosphatase.
†Sotalol has both class II and III actions.

76.1% of patients (95% CI, 72.8 to 79.4) being in sinus rhythm at 24 h posttherapy. The treatment benefit of propafenone vs placebo was greatest in the first 8 h after treatment (treatment benefit, 32.9%; 95% CI, 24.3 to 41.5; p < 0.01).

Several RCTs[27–33] have compared the effect of propafenone with placebo as well as other AADs in conversion to sinus rhythm in patients with acute AF (Table 4). All RCTs found that propafenone, either oral or IV, was more effective than placebo in converting a greater proportion of patients back into sinus rhythm.

The efficacy of propafenone has also been investigated taking into consideration the influence of age in AF. Boriani et al[34] conducted a single-blind placebo-controlled RCT of 240 patients with recent-onset AF (< 7 days) and randomized patients to either a single oral dose of propafenone, 600 mg, or placebo. Furthermore, the groups were divided by age with a cutoff of 60 years. After 8 h of follow-up, the likelihood of conversion to sinus rhythm was significantly greater in both age groups in the propafenone treatment arms. The corresponding odds ratios were 4.74 (95% CI, 2.12 to 10.54; p = 0.02) and 6.75 (95% CI, 3.28 to 73.86; p = 0.01) in patients < 60 and > 60 years of age, respectively.

Furthermore, logistic regression analysis showed the conversion to sinus rhythm within 8 h was more likely in those age < 60 (p = 0.0467).

Bianconi et al compared propafenone with digoxin in a single-blind placebo-controlled RCT.[35] The 123 patients with AF (< 72 h duration) were randomized to IV propafenone (2 mg/kg), IV digoxin (0.007mg/kg), or placebo. After 1 h, nonconverted patients in the active treatment group received the alternative active therapy and those in the placebo group were further randomized to receive one of the active therapies. The end of follow-up was at 2 h. At 1 h, 49%, 32%, and 14% of patients converted to sinus rhythm in the propafenone, digoxin, and placebo groups, respectively. Propafenone was significantly better than digoxin (p = 0.12) and placebo (p < 0.001). After the crossover period, a further 48% of patients given propafenone converted to sinus compared to 5% who were given digoxin (p < 0.05). Furthermore, of the nonconverted patients having received placebo, sinus rhythm was obtained in 53% of those having received propafenone compared to 5% having received digoxin (p < 0.05).

From these RCTs, propafenone appears to be significantly better than placebo in the pharmacologic conversion of acute AF to sinus rhythm as

Table 2—AADs in Acute AF

Drug	Dose for Conversion	Dose for Maintenance	Comments
Flecainide	200 mg orally, repeat after 3–4 h (IV 2 mg/kg)	50–150 mg bid	Only for use without structural heart disease
Propafenone	600 mg orally (IV 2 mg/kg)	150–300 mg bid	As for flecainide
Sotalol	5–10 mg slowly IV, may be repeated	120–160 mg bid	Conversion rate is slow; proarrhythmia risk is high
Amiodarone	6 mg/kg bolus over 30–60 min, then 1,200 mg IV over 24 h	600 mg daily 1 wk, follow by 400 mg daily 1 wk, thereafter 200 mg daily	Moderately effective, slow onset, good heart rate control; hypotension with bolus dose

Table 3—*Randomized Control Trials on Flecainide Compared With Placebo and Other AADs**

Study/Year	No. of Patients	AF Onset	Comparison	Result (Time); p Value
Donovan et al[21]/1995	98	72 h	IV flecainide vs IV amiodarone vs placebo	59% vs 34% vs 22% (2 h); p = 0.007
Donovan et al[22]/1992	102	72 h	IV flecainide vs placebo (digoxin added to all digoxin naive patients)	67% vs 35% (6 h); p = 0.003
Martinez-Marcos et al[23]/2000	150	48 h	IV flecainide vs IV propafenone vs IV amiodarone	90% vs 72% vs 64% (12 h); p = 0.008 for the overall comparison, p = 0.002 for flecainide vs amiodarone, p = 0.022 for flecainide vs propafenone, and p = 0.39 for propafenone vs amiodarone
Capucci et al[24]/1992	62	Up to 1 wk	1) Flecainide vs amiodarone vs placebo 2) Flecainide vs amiodarone	1) 91% vs 37% vs 48% (8 h); p < 0.01 2) 95% vs 89% (24 h); p = insignificant; conversion time was shorter for flecainide

*Outcome is conversion to sinus rhythm.

compared to placebo, although these benefits are not evident in comparison to other AADs. However, in such studies treatment with propafenone appeared to be quicker at restoring sinus rhythm.

Taking into consideration the benefits of propafenone, there have been further studies investigating the risks associated with its use. The Safety Antiarrhythmic Therapy Evaluation (SATE) trial[36] recruited 246 patients with AF (< 48 h duration). Patients were randomized to receive digoxin and quinidine, propafenone, propafenone and digoxin, or placebo. The results of this study confirmed a good safety profile of propafenone, and no significant differences were detected in adverse events between all study groups. Podrid et al conducted a longer study investigating the safety of propafenone in patients with supraventricular tachycardia, atrial flutter, and AF.[37] The 480

patients were followed up over a mean of 14.4 months. Although propafenone was associated with cardiovascular toxicity including arrhythmia aggravation, congestive heart failure, and conduction disturbances, this was more likely to occur in patients with underlying heart disease (20% vs 13%). Although 17% of patients had cardiovascular toxicity, only 4% required discontinuation of therapy. The results of these trials confirm the safety findings in the other RCTs investigating propafenone.

Class II (β-Blockers)

Timolol: Timolol is rarely used in clinical practice nowadays, but the RCT data for this agent can be translated to the effects of old β-blockers. We found one double-blind placebo-controlled RCT by Sweany

Table 4—*Randomized Control Trials on Propafenone Compared With Placebo and Other AADs**

Study/Year	No. of Patients	AF Onset	Comparison	Result (Time); p Value
Boriani et al[27]/1995	87	<7 days	IV propafenone vs oral propafenone vs placebo	66% vs 69% vs 24% (8 h); p < 0.005
Botto et al[28]/1998	123	<72 h	IV propafenone vs oral propafenone vs placebo	53% vs 78% vs 48% (8 h); p < 0.03
Ganau et al[29]/1998	156	<72 h	IV propafenone vs placebo	70.3% vs 17.3% (2 h); p < 0.001
Fesco et al[30]/1996	75	<72 h	IV propafenone vs placebo	58.5% vs 29.4% (within 3 h or until conversion occurred); p < 0.01
Blanc et al[31]/1999	86	<2 weeks	Oral propafenone vs oral amiodarone	56% vs 47% (24 h); p = nonsignificant
Kochiadakis et al[32]/1998	143	<48 h	IV propafenone vs IV amiodarone vs placebo (digoxin added to all digoxin-naive patients)	78.2% vs 83.3% vs 55.1% (within 1 h); p < 0.02 (drug vs placebo)
Ramano et al[33]/2001	352	N/A	Propafenone vs flecainide vs placebo	92.1% vs 89.8% vs 46.3% (24 h); p < 0.05 (drug vs placebo)

*Outcome is conversion to sinus rhythm. N/A = not available.

et al[38] where 160 patients with supraventricular arrhythmias were randomized to receive IV timolol, 1 mg, or matching placebo. Two further doses at 20-min intervals were given if the arrhythmia had not converted to sinus rhythm. The proportion of responders (conversion to sinus rhythm or reduction of ventricular rate < 100 beats/min) was 68% after timolol and 7% after placebo. This included the subgroup analysis of patients with AF (58.6% vs 9.4%). In particular, timolol increased the proportion of patients with a ventricular rate < 100 beats/min compared with placebo (41% vs 3%; p < 0.01). The most common adverse events were of hypotension (9%) and bradycardia (2%).

Other risks of β-blocker therapy in acute AF include the precipitation of heart failure and bronchospasm.[39] Common practice in the critical care setting is to consider the use of IV β-blockers such as esmolol (which has a very short half-life) or metoprolol, for rate control. Alternatively, oral cardioselective β blockers such as metoprolol could be used.

Class III

Sotalol: Sotalol in low doses (80 to 160 mg/day) acts similarly to a standard β-blocker. In high doses (240 to 480 mg/day), especially in patients who have a low body mass index or renal impairment, this drug has class III antiarrhythmic effects. The use of sotalol has to be cautious due to its side effects, including proarrhythmia. There are no RCTs or systematic reviews that have compared sotalol with placebo for rhythm control in patient with acute atrial fibrillation. There have been a few RCTs that have compared amiodarone, sotalol, and digoxin (see amiodarone).

Amiodarone: Amiodarone is a class III AAD that is frequently used in the critical care clinical setting. There have been RCTs and a meta-analysis of RCTs to assess the efficacy of amiodarone in comparison to placebo and other antiarrhythmic agents (Table 5).[40–46]

The comparison of the efficacy of amiodarone and flecainide has been discussed previously. Although amiodarone is effective in both the rhythm and rate management of acute AF, the metaanalysis conducted by Hilleman and Spinler[41] reported significant complications with its use. Pooled estimates placed the risk of adverse events with IV amiodarone to be as high as 26.8% in placebo-controlled studies, and the most common side effects encountered were phlebitis, bradycardia, and hypotension.

Class IV

Diltiazem: A retrospective review by Wang et al[47] assessed the effectiveness of diltiazem in controlling the ventricular response in patients with rapidly conducted AF (ventricular rate > 150 beats/min). A total of 70 patients were identified. Compared to a disease-matched control group, diltiazem (mean total dose, 19.8 mg) significantly reduced the ventricular rate; the difference between the groups was 38 beats/min (95% CI, 24 to 52; p < 0.001). There was a higher chance of the diltiazem group achieving a ventricular rate reduction to 100 beats/min (odd ratios 22.6; p < 0.01).

Schreck et al compared the effectiveness of IV diltiazem with digoxin.[48] In this open-label RCT, consecutive patients with acute AF were assigned to receive either diltiazem (0.25 mg/kg initial bolus

Table 5—*Randomized Control Trials on Amiodarone Compared With Placebo and Other AADs**

Study/Year	No. of Patients	AF Onset	Comparison	Result (Time); p Value
Peuhkurinen et al[40]/2000	62	<48 h	Oral amiodarone vs placebo	87% vs 35% (24 h); p < 0.0001
Hilleman et al[41]/2002	Metaanalysis	<7 days	1) Amiodarone vs placebo 2) Amiodarone vs other AAD	Pooled cohort estimates: 1) 82.4% vs 59.7%; p = 0.03 2) 72.1% vs 71.9%; p = 0.84
Faniel et al[42]/1983	26	N/A	Patients refractory to treatment with either DCC or other antiarrhythmic agents were given amiodarone	80.8% conversion to SR within 24 h; no p value
Hou et al[43]/1995	50	<10 days	IV amiodarone vs IV digoxin	92% vs 71% (within 24 h; apparent difference seen in first hour); p = 0.0048
Hofmann et al[44]/2006	100	N/A	IV amiodarone vs IV digoxin	42% vs 18% (1 h); p = 0.012
Joseph et al[45]/2000	120	<24 h	1) Active treatment (amiodarone/sotalol) vs control group (digoxin) 2) Amiodarone vs sotalol	1) 95% vs 78% (48 h); p < 0.05 2) No significant difference
Thomas et al[46]/2004	140	N/A	IV sotalol vs IV amiodarone vs IV digoxin	44% vs 51% vs 55% (12 h); p = nonsignificant

*Outcome is conversion to sinus rhythm. N/A = not available; SR = sinus rhythm.

followed by 0.35 mg/kg 15 min after, and then an infusion of 10 to 20 mg/h to maintain a heart rate < 100), digoxin (0.25-mg boluses at 0 and 30 min), or both digoxin and diltiazem. Follow-up was for 180 min. Treatment with diltiazem achieved a rapid reduction in ventricular rate compared to digoxin, the results becoming statistically significant by 5 min (p = 0.006). Furthermore, this effect was maintained throughout the study period. The reduction in heart rate achieved with digoxin did not reach statistical significance until the end of the study period. There was no additional benefit of the addition of digoxin to diltiazem in rate control.

Verapamil: In a randomized double-blind study by Waxman et al,[49] the effectiveness of verapamil was evaluated in the control of ventricular response in patients with supraventricular tachycardia and AF/atrial flutter. Patients (n = 20) were randomized to receive verapamil (0.075mg/kg IV) or placebo. The mean ventricular rate was reduced from 146 to 114 beats/min in the verapamil arm compared to a reduction from 145 to 132 beats/min in the placebo group (p < 0.01).

Furthermore, IV verapamil was directly compared to diltiazem in a small double-blind crossover RCT by Phillips et al[50] where 17 men with AF/atrial flutter with ventricular rates > 120 were randomized to IV diltiazem or verapamil as initial boluses followed by a continuous 8-h infusion. After a washout period, the alternative therapy was administered. There were no reported significant differences in mean ventricular response between both groups of therapy.

Rate-limiting calcium channel antagonists have therefore been shown to be effective in ventricular rate reduction in acute AF. The major adverse event reported from the RCTs was the precipitation of symptomatic hypotension (18% of patients)[50]

Other Drugs Used in Acute AF

Digoxin and Cardiac Glycosides: No RCTs have assessed the efficacy of digoxin in acute-onset AF. Jordaens et al[51] investigated the cardioversion of recent onset AF (< 7 days duration) using digoxin as compared to placebo. This double-blind RCT recruited 40 patients to receive either digoxin (total IV dose of 1.25 mg in divided doses) or placebo. At 12 h posttherapy, there was no significant difference between the rates of conversion between the digoxin- and placebo-treated groups (47.4% vs 40%, respectively). However, early ventricular rate reduction was observed, and at 30 min posttherapy the mean heart rate was significantly lower in the digoxin-treated

patients (118 ± 23 vs 139 ± 33; p < 0.02). However, the persistent stable slowing of heart rate (< 100 beats/min) was only seen in 30% of the nonconverted patients randomized to digoxin at 12 h posttherapy. These results were mirrored by Falk et al[52] who conducted an RCT comparing digoxin (IV infusions of 0.6, 0.4, 0.2, and 0.2 mg consecutively at 0, 4, 8, and 14 h or until conversion to sinus rhythm was achieved) or placebo. Thirty-six patients with recent-onset AF (< 7 days duration) were included, and no difference was observed in the conversion to sinus rhythm between the two groups (50% digoxin vs 44% placebo), APR + 6%, 95% CI, 11 to 22).

A larger RCT included 239 people with recent onset AF (< 7 days duration) and compared IV digoxin (mean dose, 0.88 mg) to placebo.[53] At 16 h follow-up there was no difference in the restoration of sinus rhythm between the two groups (51% digoxin vs 46% placebo; p = 0.37). However, a significant reduction in ventricular rate was observed in the digoxin-treated group at 2 h posttherapy (105 beats/min digoxin vs 117 beats/min placebo; p = 0.0001). The comparison of digoxin to other AADs has been reviewed in previous sections.

It is important to stress that digoxin has no benefits in the conversion to sinus rhythm compared to placebo, although it has a rate-controlling effect. In the RCTs, the number of adverse events were small and related to the precipitation of bradyarrhythmias.

New Antiarrhythmia Agents: The use of current AADs are limited by suboptimal efficacy and proarrhythmia risks. As a result, novel agents are being developed with the aim of reducing the potential of cardiac and noncardiac side effects.

Ibutilide is a new class III antiarrhythmic agent that prolongs the action potential duration by enhancing sodium exchange. It has been reported to have high conversion rates for AF to sinus rhythm.[54] One study showed that ibutilide was more effective than procainamide (40% vs 20%) in the conversion of AF to sinus rhythm within 1 h.[55] Another study that compared ibutilide with amiodarone showed that the rate of conversion of AF to sinus rhythm was higher with ibutilide.[56]

A few studies have investigated dofetilide, which is a class III antiarrhythmic agent and an IKr blocker that prolongs the action potential. In the European and Australian Multicenter Evaluation Research on Atrial Fibrillation Defetilide (EMERALD),[57] dofetilide was found to be more effective in converting AF to sinus rhythm when compared with sotalol (29% vs 6%; p < 0.05). In the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide study (SAFIRE-D),[58] the

conversion rate was 32% by day 3 when compared with placebo of 1% (p < 0.001). The Danish Investigations of Arrhythmia and Mortality on Dofetilide-Atrial Fibrillation (DIAMOND-AF)[59] also showed that the rate of conversion was 59% in dofetilide patients vs 34% of placebo patients.

Azimilide is a class III agent that blocks both IKr and IKs components of the potassium channel. As a result, it prolongs the atrial and ventricular action potential duration and refractory period.[60] In the randomized controlled trials of the Azimilide Supraventricular Arrhythmia Program (ASAP), there was a 40% reduction in total asymptomatic AF episodes with azimilide when compared with placebo (p = 0.03).[61] Other clinical trials[62,63] that compared azimilide with placebo showed no significant difference in the prevention of recurrence of AF. Of note, azimilide prolongs the QTc interval.[60]

Another promising class III antiarrhythmic agent, dronedarone, blocks potassium, sodium, and calcium channels. This drug is a deiodinated analog of amiodarone with less lipophilic, and hence it has a smaller volume of distribution.[64] Two large clinical trials, the American-Australian Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) and the European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS), investigated the efficacy and safety of dronedarone. Patients who were taking dronedarone showed significant increase in the median time to first occurrence of AF or flutter as well as a significant decrease in mean heart rate during first AF recurrence when compared with placebo.[65] Another clinical trial also reported a favorable outcome on the use of dronedarone in comparison with placebo, with a 24% decrease risk of cardiovascular-related hospitalization or death and 50% AF suppression in the dronedarone group.[66]

Other antiarrhythmic agents are being developed and are under clinical investigation. The preliminary data on novel antiarrhythmic agents are promising, but further large RCTs are needed to assess long-term efficacy and safety.

Electrical Cardioversion: There are no systematic reviews or RCTs assessing the efficacy of DCC in patients presenting with hemodynamically stable acute AF. Although DCC is recommended as first-line therapy in unstable patients, guidelines advocate the use of DCC within 48 h of presentation as one of the rhythm-controlling strategies available.

Anticoagulation: Critically ill patient could develop an acute stroke due to the severe underlying pathologies, coagulation disorders, and a proinflammatory state. However, specific large studies on incidence of stroke in critically ill patients are lacking. There were two studies that assessed stroke incidence in critically ill patients: one study focused on children (n = 20),[67] and one other small study focused on adults (n = 19).[68] The development of acute AF could result in these patients being at even higher risk for stroke.

As for patients with hemodynamic instability, there are no clinical trials assessing the role of anticoagulation in acute AF. Consensus statements made by NICE and the American Heart Association/American College of Cardiology/European Society of Cardiology (AHA/ACC/ESC) guidelines advocate the use of heparin prior to cardioversion in acute AF, irrespective of the method used.

One RCT compared unfractionated heparin and low molecular weight heparin on 155 patients with AF between 2 and 19 days' duration and undergoing transesophageal echocardiography-guided cardioversion.[69] The RCT found no significant difference in rates of stroke, systemic embolism, thrombus observation, or bleeding. Use of low molecular weight heparin simplified the treatment regimen and allowed early discharge from the hospital.[70]

However, for patients with planned elective DCC, oral anticoagulation has to be initiated and therapeutic levels maintained for at least 3 weeks before and 4 weeks after the procedure. For patients who decide not to pursue DCC, appropriate thromboprophylaxis should be assessed according to their intrinsic stroke risk. The UK NICE[11] guidelines incorporate a risk stratifying schemata derived from validated stroke risk factors.[11]

Conclusion

Acute AF is rapid, irregular, and chaotic atrial activity lasting < 48 h. Most of the patients revert back to sinus rhythm spontaneously. Patients who are hemodynamically unstable with acute AF should have urgent electrical cardioversion. For patients who are hemodynamically stable, either rhythm control or rate control strategy can be used.

Flecainide, propafenone, and amiodarone increase the chance of cardioversion to sinus rhythm when compared with placebo. Both flecainide and propafenone should not be used in patients who have structural heart disease. In clinical trials, sotalol is not inferior compared to amiodarone in conversion of sinus rhythm, but the use of sotalol has to be cautious given the risk of proarrhythmia. Digoxin was found to be no better than placebo in conversion of sinus rhythm. Rate-limiting calcium channel blockers and digoxin are effective in ventricular rate reduction in acute AF.

Postgraduate Education Corner

There is consensus that antithrombotic treatment with heparin should be given before cardioversion to reduce the risk of embolism in people who are hemodynamically stable.

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