Atrial fibrillation in the intensive care setting

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Atrial fibrillation (AF) is the commonest cardiac arrhythmia both in the general population and in the intensive care unit (ICU) setting. Its incidence continues to rise, affecting up to 10% of patients admitted to a general ICU and up to 50% of those admitted to a cardiac ICU. Uncontrolled AF has detrimental effects on the cardiovascular system, including heart failure, thromboembolic events, reduced quality of life and prolonged hospital stay. This article reviews the risk factors for developing AF, possible underlying mechanisms, clinical features and diagnosis, and focuses particularly on its management according to the latest guidelines with a specific focus on the ICU patient. We also discuss novel anticoagulants that will revolutionise the management of antithrombotic therapy in AF patients by replacing warfarin.

Keywords: *atrial fibrillation; diagnosis and treatment; intensive care; review*

Introduction

Atrial fibrillation (AF) is an atrial arrhythmia that is characterised by predominantly uncoordinated atrial activation with consequent deterioration of atrial mechanical function.[1] Death, thrombo-embolic events, hospitalisation, left ventricular failure, reduced quality of life and poor exercise capacity are potential complications associated with uncontrolled or untreated AF. It affects between 1-2% of the general population and its incidence has increased over the past two decades by about 13%,[2] and is likely to increase further over the next 50 years due to the ageing population.[2] According to the Framingham Heart Study, the lifetime risk for the development of AF is 25% at the age of 40.[3] AF is more common in men, the elderly population[4] and in caucasians,[5] although studies in the non-caucasian population are limited.[2]

In the intensive care unit (ICU) setting, AF is the most common arrhythmia. This is due to a number of factors: the patients are generally more unwell, receive intravenous fluids, require inotropic support, and have a high incidence of renal failure and sepsis. The presence of AF often results in prolonged hospitalisation with a burden on healthcare resources.[6] Nevertheless, the precise prevalence of AF in general ICUs remains unclear because it has been poorly studied. Some authors have quoted an incidence between 1.8% and 10% in non-cardiac patients admitted to ICU[6-8] although these observations related to the incidence of a variety of atrial tachycardias, not only AF. One prospective, observational study found the incidence of AF to be 7.8% in patients admitted to a non-cardiac surgical ICU.[7] Another prospective study found AF in 5.3% of surgical ICU patients, and identified age, blunt thoracic trauma, shock, the presence of a pulmonary artery catheter and previous treatment with calcium channel blockers as independent predictors of AF (see **Table 1**).[6] More recently, a retrospective observational study of three mixed medical and non-cardiac surgical ICUs revealed an incidence of new onset AF of around 4.5%.[8]

Predictors of atrial fibrillation	Odd ratio (95% confidence interval)
Age	1.04 (1.01-1.07)
Blunt thoracic trauma	16.84 (4.00-71.20)
Shock	6.77 (2.17-21.12)
Pulmonary artery catheter	5.46 (1.84-16.21)
Previous treatment by calcium-channel blockers	3.87 (1.18-12.74)

Table 1 Multivariate predictors of atrial fibrillation.[6]

The incidence of AF becomes even more significant on cardiothoracic ICUs, where it is the most common complication after cardiac surgery;[9] in fact, it occurs in 30% of patients post-coronary artery bypass graft (CABG) surgery,[10,11] in 40% of cases following cardiac valve surgery[12] and in 50% of subjects after CABG plus valve surgery.[12,13]

Due to its impact on morbidity and mortality, AF places a significant burden on NHS costs and resources. Greater emphasis should be placed on its diagnosis and treatment and even more importantly on the prevention of this atrial arrhythmia. This article reviews the latest guidance on managing AF and focuses particularly on AF presenting in the ICU patient, highlighting risk factors, clinical presentation, diagnosis and treatment.

Risk factors for developing AF and potential mechanisms

In the past, AF not related to any obvious underlying cause (such as ischaemic heart disease or hypertension) was termed idiopathic atrial fibrillation. However, with the realisation that AF can be attributed to a number of different causes, the

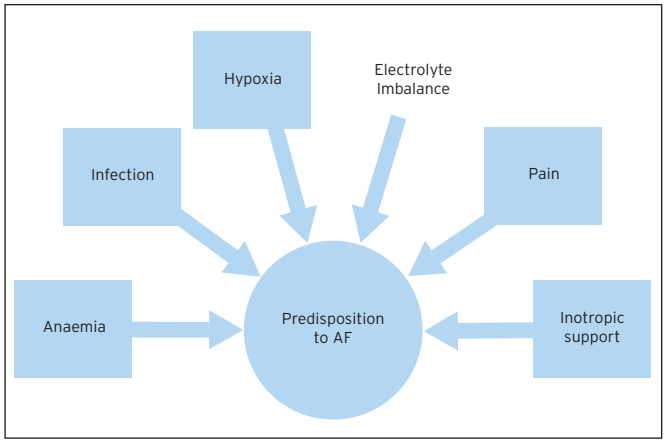


Figure 1 Predisposing factors for developing AF in the ICU setting.

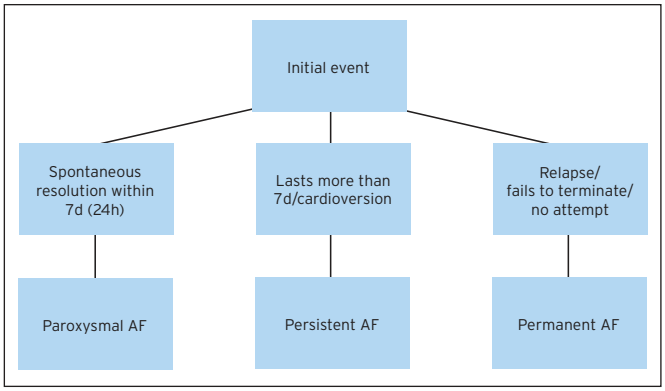


Figure 2 Classification of AF.

diagnosis of idiopathic AF has become less common and the definition of 'primary' or 'lone' atrial fibrillation has been introduced to indicate those cases of AF not associated with any underlying heart disease.[14] The incidence ranges between 1.6-30% depending upon the patient population studied.[15]

Risks factors for the development of AF differ between the general population and those patients admitted to the ICU, particularly in subjects following cardiac surgery. Common aetiological factors in the non-ICU population include age, ischaemic heart disease, hypertension, rheumatic heart disease, thyrotoxicosis, cardiomyopathy, mitral valve pathology, haemochromatosis and infection.[16]

In the limited number of observational studies performed in the ICU setting, most authors have suggested that AF tends to be more common in older subjects[17] due to the increased susceptibility of older atria to develop atrial arrhythmia.[18] The underlying mechanism is related to the increased length and dispersion of atrial refractoriness that dampens the recovery of atrial excitability in the older atrium.[19] It has been found also that with time, the conducting system, together with atrial shape and volume, is altered by the processes of atrophy and fibrosis, which ultimately results in a higher incidence of AF among the elderly population.[12]

There is also increasing evidence that systemic inflammation might play an important role in the pathogenesis of AF, particularly in the ICU setting. In a prospective observational study involving septic patients who developed AF on a general surgical ICU, Meierhenrich and colleagues[7] reported an elevation in C-reactive protein (CRP) levels before the onset of AF, which was independent of the risk factors already mentioned for the non-ICU population. In a study conducted by Chung and colleagues,[20] patients with AF had a two-fold higher level of CRP than their control counterparts, and patients with persistent AF had a higher CRP when compared with those with paroxysmal AF suggesting a role for inflammation in maintaining AF.[20]

The autonomic nervous system has been thought to be involved in the pathogenesis of AF.[21] Increased sympathetic tone (for example, secondary to operative stress, anaemia, trauma or pain) can initiate atrial automatic potentials and sustain them by lowering the atrial refractory period, resulting in micro re-entry.[22-24] Similarly to the non-ICU population, hypertension has been found to be associated with an increased risk of developing AF in the ICU setting; in several observational studies on patients with septic shock, new-onset AF was more prevalent in subjects who were older and had a history of hypertension both in cardiac[12] and non-cardiac ICUs.[7] Previous authors[6,25] reported that patients who developed AF on a surgical ICU had a high prevalence (37.5%)[6] of arterial hypertension.

Other important aetiological factors such as ischaemic heart disease, pre-existing heart failure, valvular heart disease, hypovolaemia[6] and electrolyte imbalance (hypokalaemia or hypomagnesaemia)[26] (see **Figure 1**) have also been related to the onset of AF in the critically ill patient, although results in some studies have been inconclusive.[7] For example, Meierhenrich *et al*[7] reported that only a small proportion of patients who developed new-onset AF had pre-existing heart failure (5%), ischaemic heart disease (21%) or valvular heart disease (5%). These authors were unable to reveal any electrolyte disturbances when new-onset AF occurred.[7]

Finally, a significant proportion of ICU patients have central venous catheters and these have been recognised as a possible cause of AF in this population.[27] Seguin and colleagues[6] found AF to be observed more frequently in patients with central venous catheters and hypothesised that the mechanical irritation of the right atrium caused by the insertion of central lines could be the underlying mechanism.

In ICU patients, those admitted following cardiac surgery represent a specific subgroup in terms of aetiology and management of AF. Specific risks associated with the development of AF following cardiac surgery include: right coronary artery stenosis, rheumatic heart disease, left ventricular hypertrophy, type of cardiac surgery, prolonged surgery and aortic cross-clamp time,[11,13] and increased automaticity (ie the self-activation of cardiomyocytes via spontaneous action potentials[28]). The use of catecholamines, particularly on the cardiac ICU, can play an important role in the pathogenesis of AF due to increased adrenergic stimulation, although results in this regard have been controversial.[7,17]

Clinical features and diagnosis

The ICU patient may have pre-existing AF or develop AF while on the unit. In the latter case, as for non-ICU patients, it may self-terminate within seven days (paroxysmal AF), last longer and therefore require intervention (persistent AF), or fail to

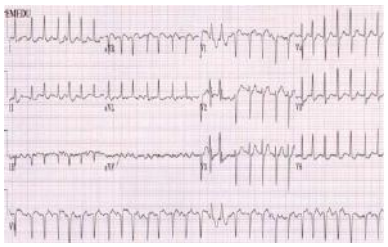


Figure 3 Typical ECG appearance of AF.

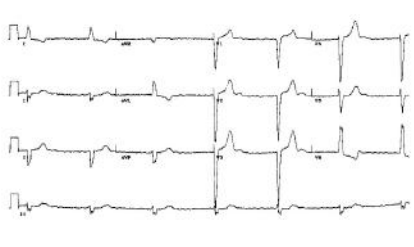


Figure 4 AF with complete heart block.

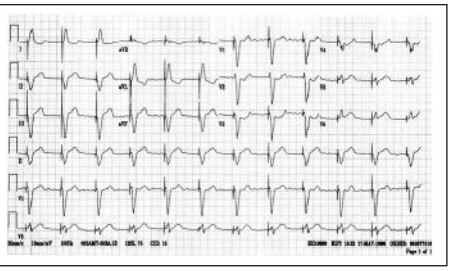
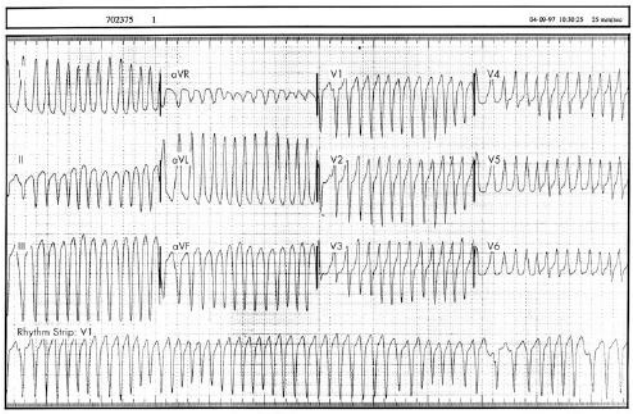


Figure 5 AF with ventricular pacing.



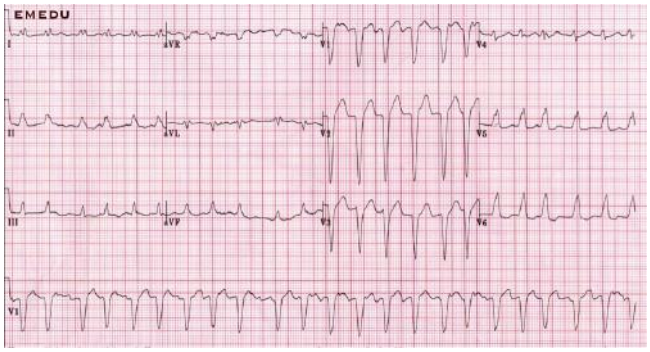


Figure 6 Example of broad complex tachycardia (left) induced by AF in the presence of aberrant conduction (left bundle branch block, right).

terminate and/or relapse within 24 hours of cardioversion (permanent AF, see **Figure 2**).

AF has a heterogeneous presentation both in non-ICU and in ICU subjects. Patients with AF may be asymptomatic or experience symptoms of palpitations, dyspnoea and/or chest discomfort, or may present with cardiovascular collapse,[29] likely due to a combination of rapid ventricular rate and the loss of the atrial contribution to ventricular filling in diastole. Pre-existing cardiovascular status is an important factor that contributes to the ill effects of AF on these patients and the loss of the 'atrial kick' may lead to a decrease in the cardiac output and up to a 50% reduction in blood pressure, which in conjunction with impaired left ventricular function may ultimately lead to cardiovascular compromise.[30]

Under resting conditions, atrial contraction accounts for about 10% of ventricular filling, but this is increased to about 40% during exercise, when the heart rate is increased and ventricular filling time is reduced, therefore having a significant impact on ventricular stroke volume, cardiac output and thus tissue perfusion and oxygenation.[31] In the presence of cardiac disease such as ventricular hypertrophy (as in aortic stenosis or hypertrophic cardiomyopathy, for example), where compliance is attenuated, increased ventricular stiffness impairs passive filling and atrial contraction contributes significantly to ventricular filling even at rest. Therefore AF can affect resting cardiac output[31] as well as cardiac output on exercise.

Less commonly, the first presentation of AF in ICU patients as well as in non-ICU patients might be directly related to its complications, including stroke or systemic embolism. In patients admitted to ICU following major cardiac surgery, AF has its highest incidence 2-4 days post-surgery.[11] These patients have a higher mortality rate, longer ICU stay and extended hospital stay.[32]

ECG characteristic of AF	Consideration
Absence of P wave Baseline fibrillatory Variable R-R interval	Typical AF
Regular R-R interval	Conduction disease AV nodal blocking agent Ventricular pacing
Irregular broad complex tachycardia	AF with aberrant conduction AF with an accessory pathway

Table 2 ECG presentations of AF.

Clinical examination, 12-lead electrocardiogram (ECG) recordings and continuous cardiac telemetry are the most frequent methods for detecting AF on the ICU. In a prospective observational study of 4,657 patients undergoing CABG surgery, diagnoses of AF by these three approaches were 12.8%, 17.5% and 76.8%, respectively.[11] On the ECG, AF is characterised by the absence of P-waves, the presence of rapid fibrillatory waves, which are variable in size, the shape and timing of which is associated with an erratic ventricular conduction in the presence of an intact atrio-ventricular (AV) node (see **Figure 3** and **Table 2**).[33,34]

In AF, the R-R interval varies due to variable AV-nodal conduction, therefore vagal and sympathetic tone and drugs affecting AV-nodal conduction (beta-blocking agents, non-dihydropyridine calcium channel blockers and cardiac glycosides) can affect the ventricular response.[35] Less

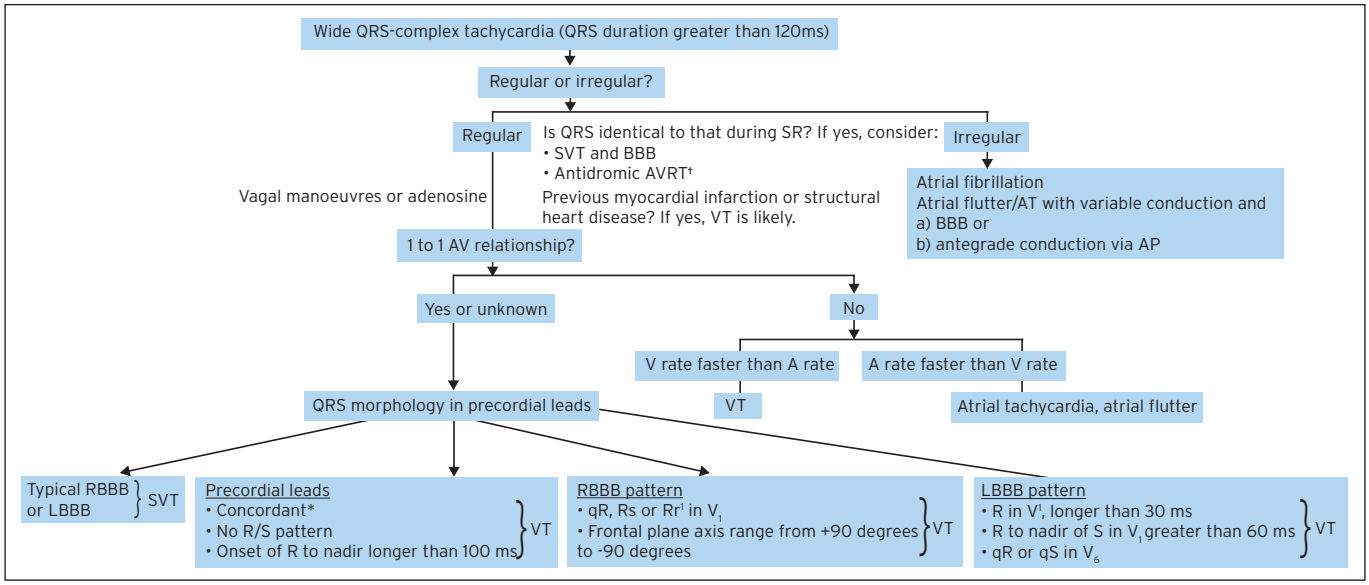


Figure 7 Brugada criteria for distinguishing between supraventricular tachycardia and ventricular tachycardia.[60] *Concordant indicates that all precordial leads show either positive or negative deflections. Fusion complexes are diagnostic of VT. †In pre-excited tachycardias, the QRS is generally wider (ie, more pre-excited) compared with sinus rhythm. A indicates atrial; AP, accessory pathway; AT, atrial tachycardia; AV, atrioventricular; AVRT, atrioventricular reciprocating tachycardia; BBB, bundle-branch block; LBBB, left bundle-branch block; ms, milliseconds; QRS, ventricular activation on ECG; RBBB, right bundle-branch block; SR, sinus rhythm; SVT, supraventricular tachycardias; V, ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.

Outcome	Rate/severity
Death	Doubled
Stroke	Increased and more severe
Hospitalisation	More frequent
Quality of life and exercise capacity	Wide variation. AF-related symptoms can be very distressing
Left ventricular function	Wide variation from nothing to tachy-cardiomyopathy and acute failure

Table 3 Relative rates and severity of outcomes in AF patients compared to the general population.

commonly, in complete heart block associated with drug therapy or conduction disease, regular R-R intervals may occur (see **Figure 4**), and in patients with permanent ventricular pacing (see **Figure 5**), the pacemaker may have to be temporarily disabled in order to visualise the underlying AF.[36] Finally, in an irregular broad-complex tachycardia (BCT) (see **Figure 6**), AF with aberrant conduction should always be suspected. It is important to distinguish BCT due to ventricular tachycardia from supraventricular tachycardia with aberrant conduction[34] (see **Figure 7**).

Clinical outcomes associated with AF

Complications associated with AF include death, thrombo-embolic events, hospitalisation, left ventricular failure, reduced quality of life and poor exercise capacity (see **Table 3**). The mortality rate of patients in AF is twice that of the general population.[2] Published observational studies of AF in ICU patients suggest that there is an increase in mortality.[17,36] AF was observed in the sickest patients and carried a higher mortality in one prospective observational study conducted in trauma patients. The same study also found that the standardised mortality ratio was comparable in both AF and non-AF patients, suggesting that AF is a marker of severity of disease without major impact on mortality.[37] Braithwaite and colleagues[17] found that ICU patients who developed atrial arrhythmias following major non-cardiothoracic surgery had higher 30-day mortality (23% *vs* 4.3%), although most of these patients died of non-cardiac causes such as malignancy or sepsis. The same group also found that these patients have a longer ICU (8.5 *vs* 2 days) and hospital stays (23.3 *vs* 13.3 days). In a retrospective data analysis based on septic ICU patients with AF on a mixed medico-surgical unit, Christian and colleagues[38] found the mortality rate to be higher (68.8% *vs* 39.8%) and the length of stay on ICU to be greater when compared to those without AF (17.7 days *vs* 8.3 days). They also found that patients with AF have an increased duration of mechanical ventilation (15 days *vs* 9.7 days). In another retrospective, population-based study, Walkey and colleagues[39] found that patients with severe sepsis with new-onset AF have an increased risk of in-hospital ischaemic stroke and mortality when compared with severely septic patients without new-onset AF (2.6% *vs* 0.6% and 56% *vs* 39% respectively). No difference in in-hospital ischaemic stroke risk was seen when severely septic patients with pre-existing AF were compared with those without AF.

AF is an independent risk factor for ischaemic stroke, with an annual risk of 4-5% up to 12% in patients with a history of previous stroke or transient ischaemic attack (TIA);[40] one in five of all strokes is attributable to this arrhythmia. In acute stroke patients, systematic cardiac monitoring would identify AF in 1 in 20 subjects.[2] Stroke in AF tends to be more severe and disabling compared to subjects without AF, and may lead to death.[2]

AF accounts for one-third of hospital admissions due to an arrhythmia associated with acute heart failure, acute coronary syndrome and thrombo-embolic complications. Patients with AF tend to have a poorer quality of life when compared to their healthy counterparts or those with ischaemic heart disease who are in sinus rhythm.[41] Left ventricular function is impaired due to rapid ventricular rate, loss of atrial kick and elevated left ventricular end-diastolic filling pressures.[2]

Management of AF

When managing patients with AF, it is crucial to establish its aetiology, as this can affect the treatment and have a significant impact on the possibility of curing the arrhythmia. Examples include acute myocardial infarction, acute myocarditis, acute pericarditis, acute pulmonary embolism and hyperthyroidism. Together, these represent a separate group, as AF will not have a tendency to recur should the aetiology resolve or be treated.[42]

Management varies between ICUs; a survey conducted by Kinnear *et al* confirms that an agreed consensus for the management of AF on ICUs is lacking.[43] There are no randomised placebo-controlled trials in the intensive care setting targeting AF once it has occurred, but there are trials comparing drugs that are supposed to be effective.[44] Despite the lack of guidelines, the same principles apply to ICU as to non-ICU patients. Patients should be fully anti-coagulated while they are either rate-controlled or sinus rhythm is restored.

In the cardiac ICU setting, the peak incidence of AF is between days two and four following cardiac surgery.[11] Current guidelines recommended restoration of sinus rhythm in all patients with *new-onset* AF within 24 hours. Every effort should be made to correct any predisposing factors.[45]

Cardioversion can be achieved through synchronised direct current cardioversion (DCC) or pharmacologically; DCC is indicated particularly in patients with haemodynamic compromise and has a success rate of up to 90%.[46] It is achieved by delivering an initial shock of 150 joules (biphasic) or a total of up to three shocks until the maximum power of the defibrillator is reached. This causes a general depolarisation of the excited myocardium, which in turn disrupts re-entry circuits leading to a period of asystole during which the sino-atrial node is able to re-establish its usual pacemaker activity.[16]

Pharmacological cardioversion has a lower success rate than DCC, but has the advantage of not requiring sedation or anaesthesia. The efficacy of various antiarrhythmic drugs in the ICU setting has been poorly studied, but principles applied to the non-ICU population are used in ICU patients. In the absence of structural heart disease (left ventricular dysfunction or ischaemic heart disease), flecainide is the drug of first choice and is able to establish conversion to sinus rhythm usually within one hour from intravenous (IV) administration. Similarly, propafenone, another 1C antiarrhythmic agent, should be avoided in patients suffering from severe obstructive airways as well as those with cardiac disease. In patients with evidence of structural heart disease, amiodarone is the first-line antiarrhythmic drug used, although cardioversion may occur several hours later compared to flecainide and propafenone. Therefore in the setting of the cardiac ICU, it is the most frequently used antiarrhythmic agent for AF termination. Amiodarone is frequently used in the ICU setting, as most patients have central lines and the most effective way of administration of amiodarone to gain cardioversion is via central access. Amiodarone increases the duration of the cardiac action potential and increases refractory period, thereby depressing atrio-ventricular conduction. It is not without ill effects including pulmonary (pneumonitis/fibrosis), gastrointestinal (nausea/vomiting/liver toxicity), dermatological (slate-grey appearance) and thyroid disorders.

Whether it is best to control rate or rhythm has been previously investigated with the AFFIRM[47] (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial. In this trial, treatment of AF in terms of rate *vs* rhythm control was compared and it was concluded that there was a pattern towards increased mortality (non-significant) in the rhythm-control arm that may be explained by the anti-arrhythmic drugs (AAD) used. Saksena *et al*[48] performed a sub-group analysis on patients from the AFFIRM trial looking at the AADs most widely used (amiodarone, sotalol, class IC drugs [flecainide/propafenone]) and clinical outcomes, which were a composite of mortality or first cardiovascular hospital stay (CVH). The time to first CVH was shorter for all AAD *vs* rate control and there was no significant difference in mortality between the two groups; however, amiodarone was associated with a significant increase in non-cardiovascular mortality not seen with sotalol/class 1C drugs when compared to the rate-control arm. Ibutilide and dofelitide have also been shown to covert AF to sinus rhythm but have the side effect of prolonging QT_c by around 60 ms and provoking non-sustained polymorphic ventricular tachycardia, which may require DCC; their use is therefore rare in the ICU setting.

When the patient is already known to have persistent AF without valvular disease, the same principles applied to the non-ICU population may be valid for patients in ICU patients. In these cases NICE/ESC/AHA/ACF guidelines recommend rhythm control in patients who:

- are symptomatic
- are younger
- are presenting for the first time with lone AF
- have AF secondary to a treated or corrected precipitant
- have congestive heart failure.

Rate control is indicated in all patients with persistent non-valvular AF in the following circumstances:

- Age above 65 years
- Concomitant coronary artery disease
- Contraindications to antiarrhythmic drugs
- Unsuitability for cardioversion, eg contraindications to anticoagulation: structural heart disease including mitral stenosis and left atrial diameter greater than 55 cm (which would preclude long-term maintenance of sinus rhythm), long duration of AF (usually >12 months), a history of multiple failed attempts at cardioversion and/or relapses, even with concomitant use of antiarrhythmic drugs or non-pharmacological approaches, on-going but reversible cause of AF (eg thyrotoxicosis).

It must be borne in mind that although there are national guidelines for the non-ICU population, not all principles may be relevant to the ICU patient; therefore, therapy must be

Rate lowering agent	Oral maintenance dose	Intravenous dose
β-blockers		
Metoprolol	100–200 mg od (extended release)	2.5–5 mg IV bolus over 2 min; up to 3 doses
Bisoprolol	2.5–10 mg od	N/A
Atenolol	25–100 mg od	N/A
Esmolol	N/A	50–200 µg/kg/min IV
Propranolol	10–40 mg tid	0.15 mg/kg IV over 1 min
Carvedilol	3.125–25 mg bid	N/A
Non-dihydropyridine calcium channel antagonists		
Verapamil	40 mg bid to 360 mg (ER) od	0.0375–0.15 mg/kg IV over 2 min
Diltiazem	60 mg tid to 360 mg (ER) od	N/A
Digitalis glycosides		
Digoxin	0.125 mg–0.5 mg od	0.5–1 mg
Digitoxin	0.05 mg–0.1 mg od	0.4–0.6 mg
Others		
Amiodarone	100 mg–200 mg od	5 mg/kg in 1 h, and 50 mg/h maintenance
Dronedarone	400 mg bid	N/A

Table 4 Drugs used to rate-control in AF.[2]

The CHA_2-DS_2-VASc scheme for stroke risk assessment		
Letter	**Clinical characteristics**	**Points**
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A	Age ≥75	2
D	Diabetes mellitus	1
S	Stroke/TIA/TE	2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque)	1
A	Age 65–74	1
Sc	Sex category (female)	1

Table 5 CHA_2DS_2VASc stroke risk stratification score.
0 points indicates an annual stroke risk of 1.9% (low risk) – aspirin or no anticoagulation is therefore recommended.
1 point indicates an annual stroke risk of 2.8% (moderate risk) – aspirin or anticoagulation should be recommended depending on patient preference.
2 or more points indicates an annual stroke risk of >4.0% (moderate or high risk) – oral anticoagulation should be recommended.

tailored to individual patients depending on their particular circumstances.

Rate control can be achieved using various AV-nodal blocking agents (including beta-blockers, non- dihydropyridine calcium channel blockers, digitalis glycosides) and amiodarone (see **Table 4**).

Beta-blockers are predominantly used to control the rate in AF, especially following a myocardial infarction or in a patient with stable heart failure. They should be avoided in patients with pulmonary disease or acute decompensated heart failure. There is minimal published data to suggest a role for beta-blockers in cardioversion except for one study (without a control group) where 13% of patients with AF converted to sinus rhythm using IV metoprolol.[2] In the stable ICU patient, rate control may be achieved using either oral beta-blockers or non-dihydropyridine calcium channel blockers. In the unstable patient, rapid control of ventricular rate may be achieved using either IV verapamil or metoprolol or even amiodarone (where left ventricular function is severely depressed). Beta-blockers do have a role in the prevention of post-operative AF (discussed below). There are many beta-blockers available on the market of which bisoprolol, carvedilol and metoprolol seem to be used most frequently in clinical practice. Metoprolol is more potent and effective compared to carvedilol.[49]

Prevention of post-operative AF

An important risk factor for the development of AF is the withdrawal of beta-blocker therapy prior to surgery, particularly cardiac surgery, and this should be avoided wherever possible.[2] Therapy with beta-blockers is more effective when provided both before and after cardiac surgery compared to use only before or only after surgery.[9] In a meta-analysis that included 58 studies with a total of 8,565 participants, beta-blockers had the greatest magnitude of effect across 28 trials (4,074 patients) in preventing AF following cardiac surgery when compared to sotalol, amiodarone and atrial pacing.[9] It has been suggested that treatment with a beta-blocker without intrinsic sympathomimetic activity should be commenced a week prior to surgery.[2]

Similarly, amiodarone has been shown to reduce the incidence of post-operative AF, to significantly shorten the duration of hospital stay, and to reduce the incidence of stroke and post-operative ventricular tachyarrhythmia.[50] In another study, AF occurred in fewer amiodarone-treated patients compared to placebo-treated patients.[52] Similarly the incidence of postoperative AF was reduced in patients aged <65 or >65 years old, those with CABG only, valve only or combination of both surgeries, and in patients who did or did not receive beta-blocker therapy.[51]

Sotalol has been reported to reduce the incidence of post-operative AF by more than 60% compared with placebo, but it has no impact on mortality, length of hospital stay or risk of stroke.[9] Given the class III properties of sotalol, the use of this drug places patients at risk of *torsades de pointes*, especially in those with electrolyte disturbances, therefore limiting its use on ICU.

Hypomagnesaemia has also been recognised as an independent risk factor for the development of postoperative AF.[2] A meta-analysis of 20 randomised, controlled trials (2,490 patients) showed that prophylactic IV magnesium reduced the probability of postoperative AF.[52]

Statins, partly through their pleiotropic anti-inflammatory actions,[53] have been shown to reduce the incidence of AF post cardiac surgery in several retrospective observation and

New anticoagulant agent	Randomised clinical trial	Primary outcome and main secondary outcomes	Other considerations
Dabigatran	**RELY-ON Trial** (18,113 patients with persistent AF, mean $CHADS_2$ score 2.1)	Reduced rate of stroke or systemic embolism but no difference in major haemorrhages with dabigatran 150 mg bid; similar rates of stroke and systemic embolism but lower rates of major haemorrhages with dabigatran 110 mg bid	Increased rate of myocardial infarction with both doses of dabigatran but mechanism unknown; increased rate of gastrointestinal bleeding with 150 mg bid dose
Rivoroxaban	**ROCKET-AF** (14,171 patients with AF, mean $CHADS_2$ score 3.5)	Non-inferiority in rates of all-cause stroke and non-central nervous system embolism; similar rate of major bleeding	Increased rate of gastrointestinal bleeding but lower haemorrhagic stroke
Apixaban	**ARISTOTLE** (18,201 patients with mean $CHADS_2$ score of at least 1)	Reduced rate of all stroke and systemic embolism, major bleeding, intracerebral haemorrhage; reduced rate of all-cause mortality and gastrointestinal bleeding	No significant reduction in rates of ischaemic stroke or cardiovascular mortality
Edoxaban	**ENGAGE AF TIMI-48** (20,000 patients with AF at risk of stroke)	In progress	In progress

Table 7 Studies investigating clinical outcomes in AF patients treated with novel anticoagulant agents when compared to warfarin.

randomised controlled studies.[54] Through the same mechanism, the use of corticosteroids has also been shown to reduce the incidence of postoperative AF,[55] however their use in ICU has been limited due to the risk of delay in wound healing, infection and altered glucose metabolism.

Anticoagulation in AF

With either rhythm or rate control, prophylaxis of thrombo-embolic events is the second main challenge encountered in the management of AF, both in the non-ICU population and in the ICU setting. Cardio-embolic stroke is the most devastating complication of AF, with an annual risk of 4-5% and approximately 12% for patients with a previous history of stroke or TIA. This risk of stroke in non-valvular AF with the subsequent appropriate anticoagulation choice can be assessed using the CHA_2DS_2VASc score, which is derived from the $CHADS_2$ score, with the addition of intermediate age (65-74 years), advanced atherosclerosis and female sex (see **Table 5**). Chronic oral anticoagulation therapy with warfarin is indicated when the score is ≥2, aimed at achieving an International Normalised Ratio (INR) of 2.5. Aspirin may be indicated instead in low-risk patients presenting with a CHA_2DS_2VASc score of ≤1.

In ICU patients, thromboembolic risk stratification is applied with similar principles and can be achieved with either warfarin, low-molecular-weight heparin (LMWH) or unfractionated IV heparin (UFH), or a combination of these.[56] Particularly in patients with *de novo* AF following cardiac surgery, current guidelines recommend that full anticoagulation should be commenced within 48 hours of the onset of AF, due to doubling of the risk of stroke.[45]

For the last six decades, warfarin has represented the cornerstone of long-term anticoagulation therapy in patients with AF, although it is associated with an increased bleeding risk including intracerebral haemorrhage (0.3-0.6%/year versus 0.15% in the non-ICU population with a mean age of 70 years),[57] particularly in patients with hypertension, abnormal liver or renal function, previous stroke, bleeding history or anaemia, labile INR, advanced age and with concomitant use of aspirin or other anti-inflammatory agents or alcohol (see **Table 6** for bleeding risk stratification). Moreover, warfarin use can be complicated by multiple interactions with food and other drugs, the need for frequent laboratory monitoring and by high rates of discontinuation. In view of these limitations, novel oral anticoagulants for thrombo-prophylaxis in AF have emerged, including direct thrombin (Factor IIa) inhibitors (eg dabigatran) and Factor Xa inhibitors (eg rivaroxaban, apixaban, edoxaban). **Table 7** illustrates the major randomised clinical trials comparing clinical outcomes of new anticoagulant agents with warfarin. In brief, dabigatran use is now licensed for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more of the following risk factors:[58]

The HAS-BLED bleeding risk score

Letter	Clinical characteristics	Points
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age >65)	1
D	Drugs or alcohol (1 point each)	1 or 2

Table 6 The HAS-BLED bleeding risk score estimates the one-year risk for major bleeding (intra-cranial haemorrhage, hospitalisation, drop in Hb 2 g/dL or more and/or need for blood transfusion:
0-2 points indicates an annual bleeding risk between 1.02-1.88% (low risk) – anticoagulation can therefore be safely recommended.
3 points or above indicates an annual bleeding risk of 3.74% or greater (moderate-high risk) necessitating cautious use and more frequent review of oral anticoagulation therapy.

- Previous stroke
- TIA or systemic embolism
- Left ventricular ejection fraction below 40%
- Symptomatic heart failure, New York Heart Association (NYHA) class 2 or above
- Age 75 years or older
- Age 65 years or older with one of the following: diabetes mellitus, coronary artery, disease or hypertension.

Rivaroxaban is recommended in patients with non-valvular atrial fibrillation with one or more risk factors:[59]

- Congestive heart failure
- Hypertension
- Age 75 years or older
- Diabetes mellitus
- Prior stroke or TIA.

Importantly none of these new agents has been investigated in the setting of ICU and therefore they are not yet in use in this category of patients, for whom warfarin with or without LMWH or UFH remains the cornerstone in the prevention of stroke and systemic embolism in non-valvular AF.

Conclusions

AF is the commonest cardiac arrhythmia and its incidence continues to rise both in the general population, due to the increased incidence of risk factors, and in the setting of ICU, due to the concomitant presence of hypovolaemia, electrolyte imbalance, central venous catheters, and so on. Patients undergoing cardiac surgery are at an increased risk of developing AF, with the highest incidence between the second and the fourth day post-surgery. Beta-blocker therapy has been shown to prevent new onset of AF in these patients. Current NICE/ESC guidelines recommend restoration to sinus rhythm within 24 hours of onset. Cardioversion can be achieved via DCC or chemical cardioversion using either flecainide (in patients with no evidence of structural or ischaemic heart disease) or amiodarone (in patients with ischaemic heart disease or left ventricular dysfunction). In the setting of cardiac ICU, amiodarone is the most frequently used antiarrhythmic for AF termination, but with the associated increase in non-cardiovascular mortality, the decision whether to use amiodarone should be tailored to the individual patient. Prophylaxis of thrombo-embolic events remains an essential component in the management of these patients and current internationally approved scoring systems provide a useful tool in order to risk stratify these patients and decide appropriate anticoagulation therapy. Warfarin, with or without LMWH or UFH, represents the cornerstone of thrombo-prophylaxis, although its use is associated with multiple food and drug interactions, most importantly with a significant increased rate of major and minor bleeding, particularly intracranial haemorrhages. Regular monitoring is essential with its use. Novel direct Factor IIa or Factor Xa inhibitors have been approved for the prevention of stroke and systemic embolism in patients with non-valvular AF in the general population, but their use has not yet been investigated in the ICU setting. Reducing the risk factors associated with an increased incidence of AF and the introduction of novel antiarrhythmic and anticoagulants agents represent the most significant challenge encountered in the management of non-valvular AF in ICU patients.

Declaration of conflict of interest

None declared.

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