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REVIEW

Twenty-five years in the making: flecainide is safe and effective for the management of atrial fibrillation

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Atrial fibrillation (AF) is the most common arrhythmia in clinical practise and its prevalence is increasing. Over the last 25 years, flecainide has been used extensively worldwide, and its capacity to reduce AF symptoms and provide long-term restoration of sinus rhythm (SR) has been well documented. The increased mortality seen in patients treated with flecainide in the Cardiac Arrhythmia Suppression Trial (CAST) study, published in 1991, still deters many clinicians from using flecainide, denying many new AF patients a valuable treatment option. There is now a body of evidence that clearly demonstrates that flecainide has a favourable safety profile in AF patients without significant left ventricular disease or coronary heart disease. As a result of this evidence, flecainide is now recommended as one of the first-line treatment options for restoring and maintaining SR in patients with AF under current treatment guidelines. The objective of this article is to review the literature pertaining to the pharmacological characteristics, safety and efficacy of flecainide, and to place this drug in the context of current therapeutic management strategies for AF.

Keywords Atrial fibrillation • Flecainide • Sinus rhythm maintenance • Remodelling • Safety • Cardioversion

Introduction

Atrial fibrillation (AF)—a supraventricular tachycardia with rapid uncoordinated atrial activation and a beat-to-beat irregular, frequently rapid ventricular rate—is on the increase, to an extent that cannot be fully accounted for by factors such as an ageing population or an increasing prevalence of cardiovascular disease.[1,2]

Current guidelines for the treatment and management of AF recommend heart rate or rhythm control, plus concomitant antithrombotic therapy.[3,4] The decision regarding which strategy to pursue is dependent on several factors, including the pattern of presentation and the presence, or lack of, underlying conditions. The latest algorithms recommend initially controlling the ventricular rate—based primarily on results of randomized trials that found no mortality or morbidity advantage of either strategy.[5] The same guidelines, however, direct that prior to choosing long-term rate control, the future effects of permanent AF should be considered. It is important to ensure that a window of opportunity to maintain sinus rhythm (SR) is not overlooked early in the course of AF management.[3] In a recent position paper it was proposed that certain patients with AF, in whom SR maintenance strategy is selected, may benefit from earlier cardioversion.[6] This was prompted by the growing recognition of the importance of structural changes that precede the first-documented AF episode. Only further studies will provide the solid data needed to test this hypothesis.

The burden of atrial fibrillation

The prevalence of AF increases with age; it is estimated that 70% of AF patients are between 65 and 85 years old (median: 75 years).[3] The impact of AF on morbidity and mortality has been thoroughly documented. The Euro Heart Survey 1 year follow-up data for 80% of the 5333 participants found that, in patients with permanent AF, the mortality rate was 8.2%. Furthermore, the mortality rate in

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patients with first-detected AF was 5.7%.[7] A strong association ($P < 0.0001$) between the maintenance of SR and overall survival was shown in a sub-analysis of the AFFIRM study.[8] The burden of AF also negatively impacts patients' quality of life (QOL); for example, patients can experience palpitations both during exercise and at rest, and have reduced physical ability,[9] forcing them to restrict their lifestyles.

Untreated and/or previously undetected episodes of AF induce electrophysiological and structural changes to the cardiac muscle, making SR restoration increasingly difficult. This vicious cycle that contributes to the AF continuum is now described as 'AF begets AF'.[10–14] In long-term follow-up studies significant proportions of patients with paroxysmal (intermittent) AF progressed to persistent (chronic) AF.[15,16] Hobbs *et al.*[17] showed that electrical remodelling in AF can be reversed in some patients if SR is maintained from an early stage, suggesting that prompt recognition and management of AF is critical.[6]

Objectives of this review

Flecainide has been available in Europe since 1982. The Cardiac Arrhythmia Suppression Trial (CAST) results, published in 1991, showed increased mortality in patients surviving myocardial infarction (MI),[18] and caused sales of class IC antiarrhythmic drugs (AADs) to fall dramatically (by 75%) and there has been a considerable decrease since 1995 in the prescribing of class I AADs in favour of class III AADs.[19,20] However, the use of flecainide is supported by results from many randomized clinical trials, and the drug is recommended as a first-line treatment option for pharmacological cardioversion and maintenance of SR in the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2006 guidelines as well as in the 2010 update of the ESC's European guidelines.[3,4] This review aims to examine the 27 years of accumulated data on flecainide's safety and efficacy, and place the drug in its therapeutic context. It also discusses the pharmacological characteristics of flecainide that are thought to prevent long-term structural and electrophysiological remodelling, as well as maintaining SR (Data on File. 11th Flecainide PSUR: Meda Pharma GmbH & Co KG, 19 August 2008).

Management of atrial fibrillation

Therapeutic options

Rhythm versus rate control

The options of either restoring and maintaining SR, or controlling the ventricular rate while allowing AF to persist, are not mutually exclusive.[3] In the AFFIRM study, a rhythm-control strategy did not show improved survival over a rate-control strategy in patients with AF,[8,21] although long-term SR control and anticoagulation therapy were associated with a lower risk of death.[8] Several studies, including the large, randomized controlled, PIAF, STAF, RACE, AF-CHF, HOT café, and AFFIRM trials, have shown that in elderly patients with minimal symptoms, rhythm control using AADs is not associated with improved mortality, morbidity, or QOL scores, compared with rate control.[21–29] Indeed, data from the AFFIRM study suggest that, in elderly patients with coexisting heart disease, the adverse effects of AADs may outweigh the benefits of SR restoration.[30] A meta-analysis of the RACE, STAF, PIAF, HOT CAFÉ, and AFFIRM trials confirmed that in patients with persistent AF or AF that is likely to be recurrent, ventricular rate control with anticoagulation therapy was equivalent to a rhythm-control strategy in preventing clinical outcomes.[31]

Over time, structural and electrophysiological remodelling induced by AF may lead to heart failure and intractable AF. The increasing prevalence of AF in an ageing population, in conjunction with slowly progressing conditions such as hypertension, coronary artery disease (CAD), obesity and heart failure, suggests that AF itself may be the culmination of a protracted process. From this perspective, the first-detected episode of AF is an important opportunity to prevent disease progression.

Evidence-based treatment guidelines

The 2006 ACC/AHA/ESC guidelines on AF[3] shown in *Figure 1* comprehensively outline treatment consensus, clearly delineating the appropriate options available for each of the different groups of AF patients encountered. The availability of new data from recent clinical trials prompted an update of the ESC European guidelines[4] to include dronedarone as a recommended first-line treatment option for maintenance of SR in patients with paroxysmal and persistent AF, except those patents with congestive heart failure New York Heart Association (NYHA) class III/IV or unstable congestive heart failure NYHA class II.

Focus on flecainide

Pharmacology of flecainide

Flecainide has local anaesthetic effects and belongs to the class 1C AADs that block sodium channels, thereby slowing conduction through the heart. It selectively increases anterograde and retrograde accessory pathway refractoriness. The action of flecainide in the heart prolongs the PR interval and widens the QRS complex. The effect on the JT interval is insignificant as flecainide does not lengthen ventricular repolarization.[32,33]

Pharmacokinetics of flecainide

Oral administration of flecainide results in extensive absorption (bioavailability: 90–95%). Flecainide does not appear to undergo significant hepatic first-pass metabolism; a 200–500 mg daily dose produced plasma concentrations within the therapeutic range of 200–1000 μg/L (the maximum daily dose is 300 mg).[32,33] The elimination half-life is 12–27 h.[32] Flecainide undergoes extensive hepatic biotransformation via cytochrome P450 CYP2D6; inactive metabolites are excreted mostly (85%) in urine.

Antiarrhythmic effect

At similar concentrations (half maximal inhibitory concentration [IC_{50}]: 1–2 μM), flecainide blocks the cardiac fast inward Na^+ current (I_{Na}) and the rapid component of the delayed rectifier K^+ current (I_{Kr}).[34–36] At higher concentrations (IC_{50}: 19 μM), flecainide also inhibits the late Na^+ current and other cardiac K^+

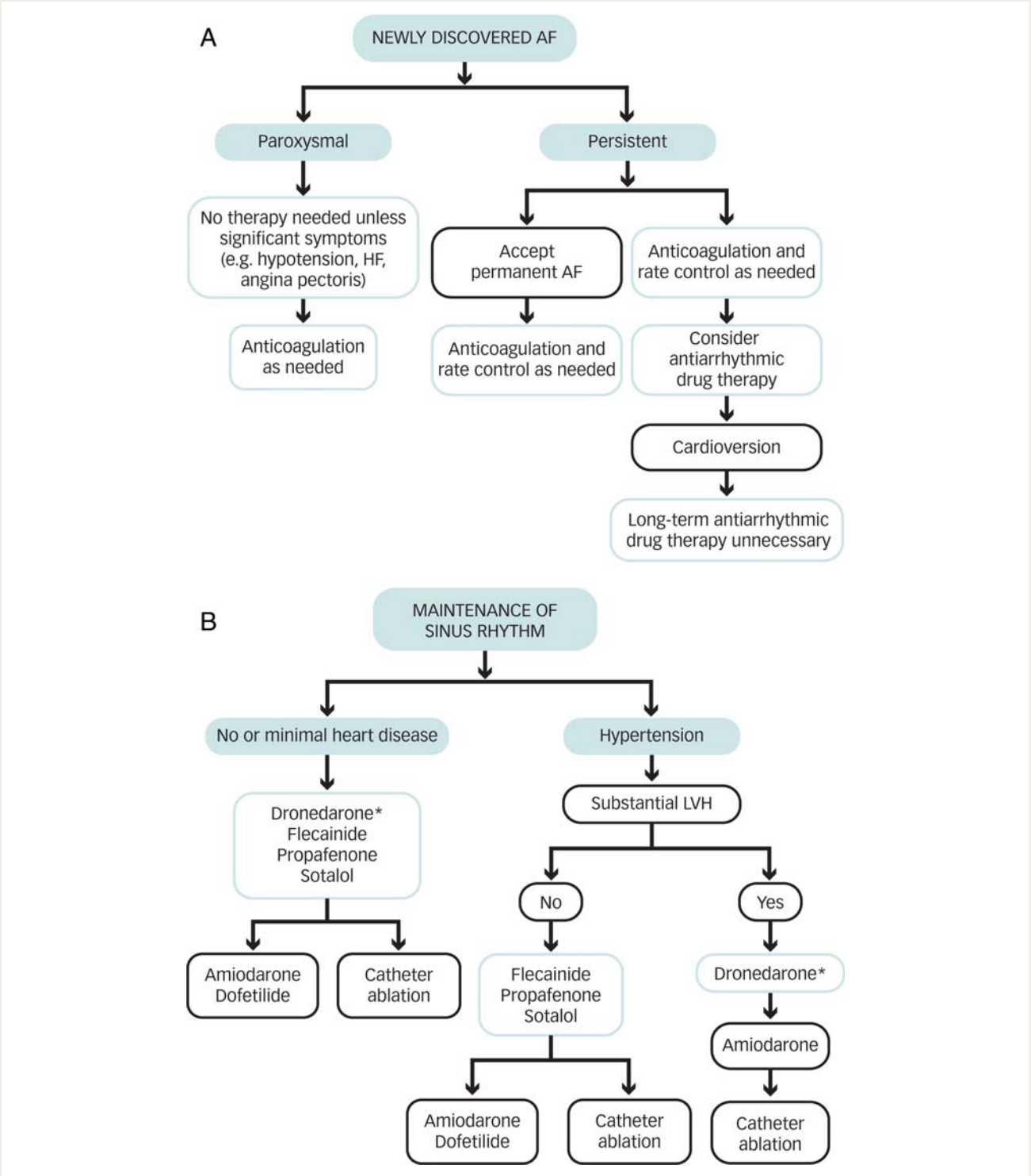

Figure 1 Evidence-based treatment guideline recommendations for (*A*) newly discovered AF and (*B*) maintenance of sinus rhythm following cardioversion (adapted from Fuster *et al.*[3]). *, Updated European Society of Cardiology recommendations[4]; AF, atrial fibrillation; HF, heart failure; LVH, left ventricular hypertrophy.

channels.[36] Flecainide has a high affinity for the open-state Na^+ channels and markedly slows the recovery time constant of Na^+ channels during diastole ($\tau > 10$ s). It has thus been classified as a class 1C AAD.[32,33,35,37–39]

Flecainide prolongs the action potential duration (APD) in ventricular and atrial muscle fibres, but shortens the APD in Purkinje fibres—an effect consistent with Na^+ channel blockade.[32,37] In human atria, flecainide only increases APD and refractoriness in

cells with a long plateau preceded by a notch.[40] Nevertheless, because flecainide exhibits very slow unbinding kinetics from the Na^+ channels during diastole, it prolongs the refractoriness to a greater extent than the APD (i.e. post-repolarization refractoriness), decreases excitability and slows intracardiac conduction, even at normal heart rates, in all cardiac tissues. Clinically, this effect seems most important at the atrial level. At the ventricular level it may cause an increase of the stimulation threshold in patients with an artificial pacemaker.

Mechanism of atrial fibrillation conversion

In superfused atrial preparations from multiple species, including dogs and humans driven at fast rates, flecainide reduces the shortening of the APD, producing tachycardia-dependent prolongation of atrial refractoriness.[41] Flecainide also suppresses atrial APD accommodation to heart rate changes in anaesthetized dogs, leading to rate-dependent prolongation of atrial refractoriness, which may be important in suppressing AF.[42] In an experimental canine models of AF, flecainide terminates AF by causing a tachycardia-dependent increase in atrial effective refractory period and wavelength, reducing the number of re-entrant circuits, so that the arrhythmia can no longer sustain itself.[43,44] However, in goats instrumented with multiple atrial electrodes, cardioversion of sustained AF induced by flecainide could not be attributed to a prolongation of atrial wavelength but to a progressive widening in the temporal excitable gap during AF.[45]

Effects on remodelling

Atrial fibrillation is known to induce significant electrophysiological alterations in atrial myocytes and causes significant structural changes (structural remodelling) in atrial tissue.[11,14,46–49] Several AF-related molecular alterations at the cellular and subcellular level are due to the activation of different signal transduction systems.[50–53] These molecular pathways are involved in the regulation of gene expression, cell proliferation, hypertrophy, fibrosis, and cell death. Histologically, fibrillating tissue shows signs of hibernating myocardium, with evidence of ischaemic or metabolic injury of the tissue, for example, disintegration of contractile filaments (myolysis), accumulation of glycogen, and mitochondrial swelling. Studies have clearly demonstrated the importance of oxidative stress for the occurrence of such changes in AF.[54,55] The increased frequency of depolarization during an AF episode causes a transient rise in Na^+ entry into atrial myocytes. Cytosolic Na^+ accumulation is believed to worsen myocardial injury, mainly as a result of increased Ca^{2+} entry through the sarcolemmal Na^+–Ca^{2+} exchanger.[56] Interestingly, Iwai *et al.*[57] reported that cytosolic Na^+ overload may directly alter mitochondrial function by depolarizing its inner membrane and reducing the rate of oxidative phosphorylation. Thus, inhibition of Na^+ channels by flecainide during rapid atrial activation should attenuate the excess cellular Ca^{2+} accumulation and reduce oxidative stress (*Figure 2*). Importantly, Na^+ enters via the fast inward Na^+ current and not the slowly inactivating component of the Na^+ current, known as the late I_{Na} (I_{NaL}), which flows during the plateau of the cardiac action potential and prolongs the QT interval. I_{NaL} is more sensitive to flecainide than I_{Na}, such that abnormal Na^+ entry via I_{NaL} can be inhibited at drug concentrations that have almost no effect on peak I_{Na}.[58]

Preliminary observations support the beneficial effect of flecainide in fibrillating human atrial tissue.[59] In an organotypic human atrial tissue model, flecainide attenuated pacing-induced oxidative stress markers and abolished the expression of hypertrophic kinases and inflammatory adhesion molecules. Thus, flecainide appears to be beneficial for ameliorating AF-induced myocardial injury and atrial dysfunction.

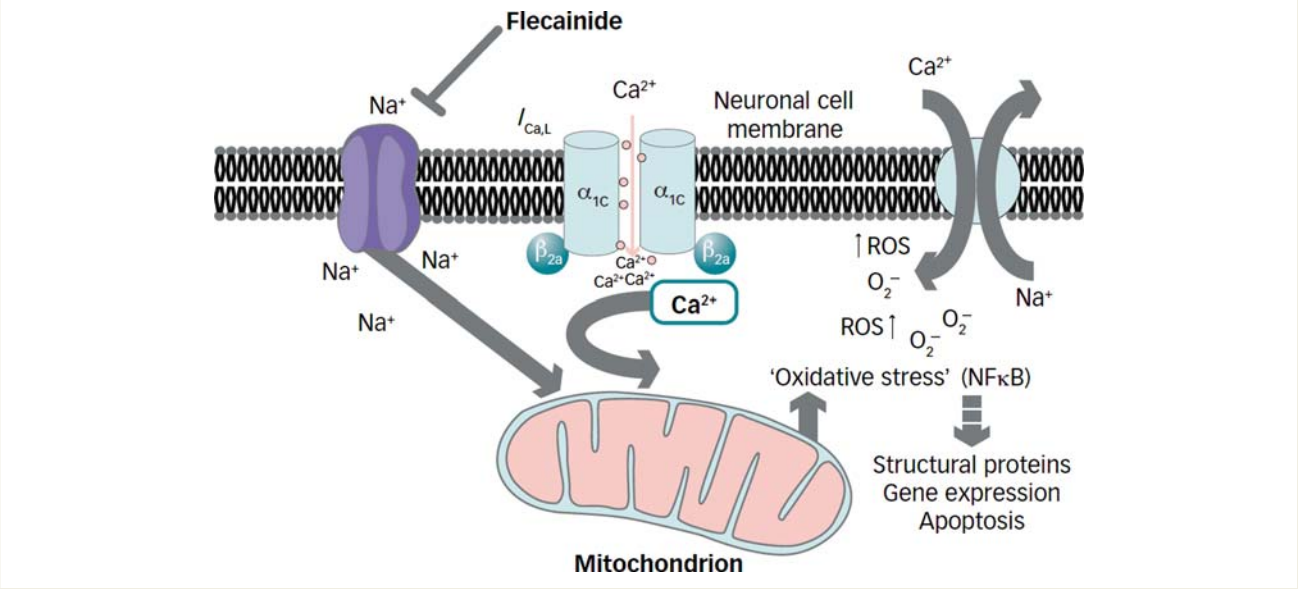

Figure 2 Inhibition of Na^+ channels by flecainide during rapid atrial activation attenuates excess cellular Ca^{2+} accumulation and reduces oxidative stress. $I_{Ca,L}$, L-type calcium current; ROS, reactive oxygen species; NFκB, nuclear factor-κB.

Electrophysiological properties

Electrophysiological studies in patients with cardiac arrhythmias demonstrate that flecainide prolongs right atrial (PA interval), atrioventricular (AV) nodal (AH interval), and His–Purkinje (HV interval) conduction times.[32,33] In patients with dual AV nodal pathways, flecainide selectively prolongs retrograde refractoriness of the fast pathway.[60,61] In patients with accessory AV pathways, flecainide slows conduction and increases anterograde and retrograde pathway refractoriness, but its effects are more pronounced on the retrograde pathway, often causing complete retrograde pathway block in patients with basal refractoriness greater than 270 ms.[60–63]

Flecainide produces a dose-dependent decrease in intracardiac conduction, but its effects on intra-atrial and AV nodal conduction are less pronounced than those on His–Purkinje conduction and ventricular activation.[32,33,60,61,64–67] It prolongs the PR (17–29%) and QT (4–11%) intervals and the QRS complex (11–27%). Most of the QT prolongation is due to a widening of the QRS complex,[32,65] so that the JT interval and the rate-corrected QT interval (QTc) remain unchanged or slightly increase (3–8%).[32,33,60,64–70] Flecainide also prolongs atrial, AV nodal and ventricular refractoriness, but its effects on refractoriness are less pronounced than its effects on intracardiac conduction.[32,60,61,64–68,70] Flecainide also increases the endocardial pacing threshold;[61] it may therefore be necessary for pacemaker-dependent patients to reprogramme their pacemaker.

Flecainide does not affect sinus rate, although bradycardia and tachycardia have been occasionally reported.[32,33] Flecainide increases the corrected sinus node recovery time and the sinoatrial (SA) conduction time in patients with sinus node dysfunction.[61,67]

Potential for proarrhythmic effects

Class 1C AADs, including flecainide, may cause supraventricular proarrhythmia during AF through a regulatory effect on atrial fibrillatory activity, leading to slow atrial flutter typically at a rate of 200 bpm (1C flutter).[71] Flecainide does not slow AV conduction and, as a result, a 1:1 ratio of AV conduction to high ventricular rate may occur. This is associated with aberrant conduction and a bizarre QRS morphology caused by exaggerated intraventricular conduction delays.[72] Atrioventricular nodal blocking drugs could be used to prevent 1:1 conduction and patients should be instructed to halt exercise when AF recurs.[3,4] Atrial fibrillation conversion to flutter is considered proarrhythmia. This effect can be useful since ablation of 1C flutter while continuing flecainide invariably leads to control of AF symptoms.[73] In addition, the danger of this type of proarrhythmia is abolished after effective right atrial isthmus ablation.

Class 1C ventricular proarrhythmia manifests as monomorphic sinusoidal wide QRS tachycardia or as polymorphic ventricular tachycardia or fibrillation. Factors associated with ventricular proarrhythmia risk include decreased left ventricular (LV) function, ventricular scar tissue, too high a dose and/or rapid dose increases. Premonitory signs on the surface electrocardiogram (ECG) include excessive increases in QRS duration.[74–76]

Late proarrhythmia is the most important threat to patients treated with AADs, especially those with supervening ischaemia or electrolyte disturbances. For class 1C drugs, CAST[77] has shown that proarrhythmia does not exclusively occur early after initiation of therapy, but may be ongoing throughout follow-up. Which factors are involved in late, out-of-hospital proarrhythmia or sudden death during 1C drug therapy is not clear. Several factors were implicated in CAST: late development of ischaemia, congestive heart failure and accumulation of the drug to toxic levels.[78] All these conditions dynamically promote Na^+ channel blockade by class I drugs. Increases in the heart rate, occurring during daily life, may set the stage for late proarrhythmia. For example, in patients with diminished LV function, during exercise there may be (sub)acute worsening of congestive heart failure, possibly due to use dependence of class I drugs.

CAST[18,77,79] results have associated flecainide with debilitating side effects and increased mortality compared with other treatment options. It is highly likely, however, that the increased mortality observed was due to a greater incidence of ventricular fibrillation in this population (the so-called proarrhythmic effect).[78] As a result, flecainide is not recommended for use in patients with CAD and/or depressed ventricular function.

Potential for haemodynamic effects

Flecainide exerts a negative inotropic effect that may relate to reduced Na^+ entry with subsequent reduced Ca^{2+} entry into the myocardial cells. In addition, it blocks the intracellular interaction between Ca^{2+} and the ryanodine receptor; new data presents flecainide as a novel strategy in preventing diastolic Ca^{2+} waves that result in triggered arrhythmias.[80] In ventricular myocytes isolated from a catecholaminergic polymorphic ventricular tachycardia mouse model, flecainide inhibited cardiac ryandodine receptor channels by open-state blockade, significantly reducing the spark Ca^{2+} mass without causing any compensatory increases in the sarcoplasmic reticulum Ca^{2+} content. Intravenous (iv) flecainide transiently reduces cardiac output and stroke volume.[81] During chronic oral therapy, flecainide has minimal effects on blood pressure,[32,40,64,69,82–84] and the LV ejection fraction (LVEF) remains unchanged, or slightly decreases, in patients with normal, or nearly normal, ventricular function.[64,68,69,85,86] However, flecainide significantly reduces stroke volume index and LVEF and increases right atrial and pulmonary capillary wedge pressures in patients with coronary heart disease,[64,68,69,84–86] acute MI,[85,87] or LV dysfunction.[84,86,88]

Initiating flecainide treatment

According to the present guidelines flecainide is indicated in patients with normal heart, hypertension, minor heart disease, and good LV function, this likely applied to some 80% of the patients with paroxysmal AF (PAF) and some 50% of the patients with persistent AF.[3,4] Overall, the 'real-life' use of flecainide is low: the Euro Heart Survey on AF indicates that around 17 and 13% of paroxysmal and persistent AF patients are treated with class IC agents including flecainide or propafenone, respectively.[89] Prior to initiating flecainide treatment, patients should be checked for contraindications including structural heart disease, second- or third-degree AV block, left bundle branch block, right bundle branch block (when associated with left hemiblock), asymptomatic non-sustained ventricular tachycardia, cardiogenic shock, reduced cardiac output (LVEF $<$ 35%), post-MI, and significant renal or hepatic impairment. Electrocardiogram parameters determined

should include PR, QT, and QRS interval prolongation (≤120 ms). In addition, the presence of ischaemia and tolerance to exercise should be determined. After initiation of flecainide, use-dependent QRS widening may be assessed during a formal exercise test. During treatment, the QRS interval should be regularly monitored.[3]

In AF, oral flecainide should be administered in a hospital setting with rhythm monitoring, starting at 50 mg BID and increased by 50 mg BID every 4 days until efficacy is achieved.[90] After administration of flecainide heart rhythm should be monitored for at least 8 h but physicians should check their local guidance for mandatory hospitalization during titration. The maximum recommended oral dose is 300 mg/day. For patients who are not able to receive high doses of standard oral flecainide and those with renal failure, a sustained-release capsule can be used. To achieve control of class IC atrial flutter, some physicians routinely use digoxin or a beta-blocker in addition to flecainide.[91]

To achieve a more rapid effect in an emergency, a bolus dose of flecainide can be administered as a slow injection of 1–2 mg/kg over 10 min, or in divided doses, up to a maximum of 150 mg, while monitoring blood pressure. If these are not effective, a continued infusion of flecainide can be given at 1.2–1.5 mg/kg/h during the first hour and 0.12–0.25 mg/kg/h during subsequent hours for no longer than 24 h. During the acute phase the QRS is usually continuously monitored but also measured with a 12-lead ECG performed at the end of bolus and at 15 min, 30 min, 1, 2, and 3 h intervals. In patients receiving higher doses, ECG and plasma-level monitoring are strongly recommended. The maximum cumulative dose over the first 24 h should not exceed 600 mg. Flecainide can also be used for hospital outpatients and in the elderly, although plasma clearance is slower than in younger individuals.

Clinical efficacy

Cardioversion

Flecainide is highly effective in the acute setting for cardioversion of AF. In haemodynamically stable patients with acute-onset AF (<48 h duration) and preserved LV function, flecainide restores SR in up to 95% of patients within 1 h from the start of the infusion. A pooled analysis of eight randomized controlled trials by the US Agency for Healthcare Research and Quality (AHRQ) showed that acute treatment with flecainide was associated with conversion rates of between 52 and 95% (*Figure 3*).[92] A further single-blind, randomized, comparative study showed that SR was achieved in 90% of patients treated with flecainide (2 mg/kg bolus, plus second bolus of 1 mg/kg if the first dose did not convert), compared with 72% of patients treated with propafenone and 64% of patients treated with amiodarone ($P = 0.008$).[93] Although patients may also spontaneously convert to SR, this

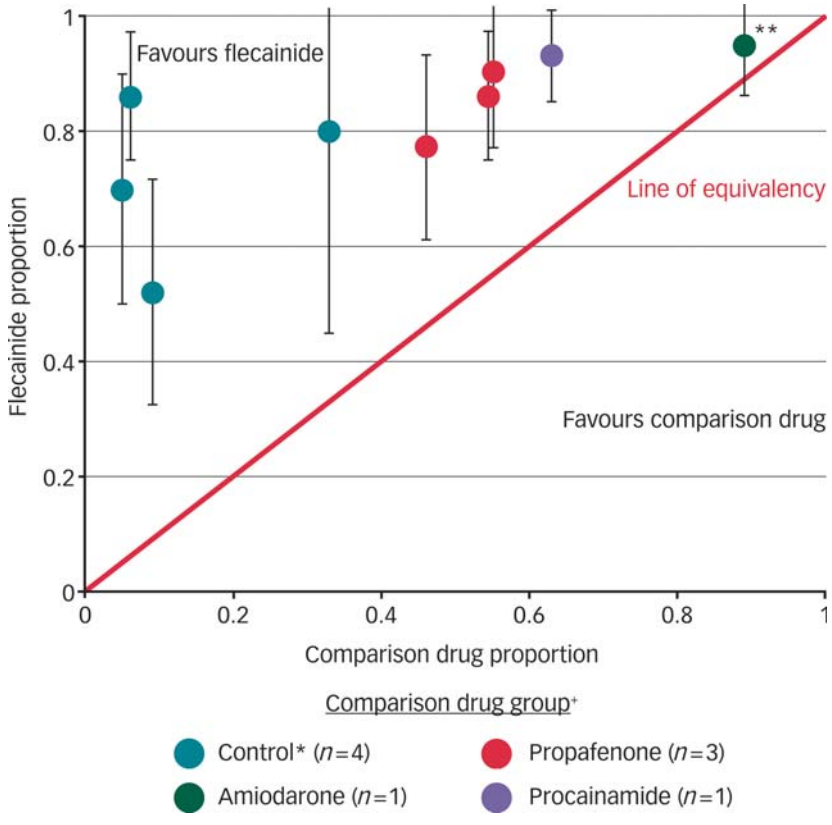

Figure 3 Proportion of subjects with successful pharmacological conversion (adapted from McNamara *et al.*[92]). *, Control treatment includes groups receiving placebo, Verapamil, diltiazem, or digoxin; **, Vertical lines represent 95% confidence intervals for the proportion of subjects with successful pharmacological conversion; +, *n* equals the number of trials evaluating each comparison.

usually takes much longer than with active iv drug. Indeed, flecainide significantly foreshortens conversion to SR. Both iv and oral flecainide can, therefore, play important roles in shortening the periods of symptomatic AF, thereby limiting complaints.[94]

Flecainide is also a safe and effective agent for termination of AF in patients with Wolff–Parkinson–White (WPW) syndrome. Classically, iv procainamide is suggested as the first-line drug,[3] but this is less effective in terminating AF. By reducing the safety of conduction over the accessory pathway, flecainide blocks conduction and slows the ventricular rate. Flecainide infusion during AF in WPW patients is therefore extremely safe. In addition to rate slowing, flecainide eventually converts AF to SR.[95]

The efficacy and safety of oral (up to 300 mg in a unique loading dose) and iv (up to 150 mg in 10 min) regimens of flecainide acetate have been clearly demonstrated (*Table 1*). In current guidelines, flecainide (oral or iv) has received a class I, level A rating for cardioversion in AF.[3] Approximately half of the responding patients convert within 3 h of the oral dose or within 1 h of the initial infusion time.[94,96–98] The single loading oral dose of flecainide has a conversion rate of 50–60% at 3 h and 75–85% at 6–8 h.[96,97,99] A loading oral dose (600 mg) of propafenone has also been shown to be effective for cardioversion of AF, with conversion rates around 72–76% at 6–8 h, although taking longer, especially in the iv infusion (3–6 h average).[99,100]

No serious adverse events were reported with regimens used when patients were ECG monitored and in a resting condition. Atrial flutter with 1:1 conduction (producing fast ventricular rates) can occur immediately before conversion with a rate of 0.2%, particularly during exercise. A long asystolic pause may also occur at the time of conversion. These constitute the main reasons for administering the first loading oral dose under strict ECG and clinical control in a hospital setting.[3,29,100]

Thereafter, a single bolus dose may be considered in an outpatient setting, after treatment has been considered safe, as a convenient method to cardiovert patients at home. This, so-called, 'pill-in-the-pocket' approach has become a means of treating patients with paroxysmal or persistent symptomatic AF with an average ventricular rate of 70/min or greater.[29] However, this strategy is only suitable for selected patients; the episode has to be of recent onset (within 48 h) in a patient with normal QRS duration and of good LV function, without SA or AV nodal dysfunction, bundle branch block, structural cardiomyopathy or Brugada syndrome. The advantage of the pill-in-the-pocket approach, despite the normally high rate of spontaneous conversion, is mainly related to the shorter time scale for conversion associated with flecainide, which may equate to a better QOL although more evidence is required.[101]

Maintenance of sinus rhythm

In PAF, flecainide has been shown to significantly reduce the number of AF recurrences, and lengthen the time between episodes.[102–107] A meta-analysis of 60 studies with flecainide showed that 65% of patients were responsive to treatment in the short-term, and 49% in the long-term, indicating that the clinical benefit of flecainide for maintaining SR is sustained.[105] A literature analysis suggests that flecainide may be more effective than several other AADs for maintaining SR following cardioversion (*Table 2*), although direct head-to-head comparisons are not available and these rates, taken with 12-lead ECGs may be higher than those seen under current monitoring guidelines.[108]

Flecainide also reduces the symptoms associated with AF; significantly more patients receiving flecainide reported suppression of palpitations ($P < 0.001$), tachycardia ($P = 0.027$), and chest pain ($P = 0.023$), compared with those receiving placebo.[102] Moreover, one out of three patients (31%) in the flecainide group reported 'complete freedom from symptoms', compared with only 9% in the placebo group.

Clinical safety

In general, class 1C AADs are associated with specific risk factors for proarrhythmic events (*Table 3*). The use-dependent electropharmacological effects are enhanced at higher heart rates; therefore, the electrophysiological effects are most marked in the atria during AF because the intrinsic atrial rate is so high. Hence, deleterious effects (e.g. ventricular proarrhythmia, negative inotropy, and AV block) are less of a risk at the doses used to stop AF. The potential downside of use dependence is that, during SR, atrial (and ventricular) effects are minor, reducing the preventative effects. However, class 1C AADs suppress premature beats, suggesting that other mechanisms, such as suppression of (abnormal) automaticity, may play a role.[32,33]

The results of CAST raised important issues regarding the safety of AADs to suppress arrhythmias or prevent arrhythmia recurrences.[18,77,79] The results of CAST deterred physicians from using flecainide, even in patients without any demonstrable cardiovascular disease. One of the most difficult issues is that patients may develop coronary disease, ischaemia and/or structural heart disease while receiving chronic flecainide. Patients who are effectively treated but who have, for example, non-significant CAD as detected by CT angiogram, may continue flecainide but should be instructed about warning symptoms, including unexplained fatigue, new or increased chest pain, or syncope. Physicians should perform an exercise test and regular ECGs, and patients should monitor their symptoms and report any problems.[109] Most importantly, background diseases such as hypertension and coronary disease should be addressed aggressively with preventative therapy once detected. Patients successfully treated with flecainide but who develop vascular disease may continue flecainide treatment if these precautions are followed.

When used in appropriately selected patients, flecainide has shown a good safety profile, as demonstrated by more than 25 years' of cumulative experience with the drug throughout the Europe and the USA. A recent systematic review determined the incidence of ventricular arrhythmias in flecainide-treated patients to be <3%.[110] A meta-analysis of 122 flecainide studies included 4811 patients with supraventricular arrhythmias but no significant signs of ventricular damage, with a mean exposure time of 241 ± 224 days. Compared with controls, flecainide was associated with a lower incidence of proarrhythmic episodes (2.7 vs. 4.8%), angina symptoms (1 vs. 1.3%), hypotension (0.8 vs. 1.3%), diarrhoea (0.7 vs. 2.8%), headache (2.0 vs. 2.9%), and nausea (1.6 vs. 1.8%).[111]

The strengths of this meta-analysis are its comprehensiveness and that all included studies were prospective; however, the

Table 1 Prospective trials on oral loading pharmacologic conversion of paroxysmal and persistent atrial fibrillation

Study	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Capucci *et al.*[97]	62 patients with recent onset AF (≤7 days), placebo versus amiodarone iv bolus followed by infusion or flecainide po	Randomized single blind trial	Conversion to SR	As a percentage	Small numbers; Placebo group discontinued monitoring after 8 h
			At 3 h	Placebo 29, amiodarone 16, flecainide 68	
			At 8 h	Placebo 48, amiodarone 37, flecainide 91	
			At 12 h	Amiodarone 47, flecainide 91	
			At 24 h	Amiodarone 89, flecainide 95	
Donovan *et al.*[98]	98 patients with acute onset AF (≤72 h), placebo vs. amiodarone iv or flecainide iv	Randomized controlled trial	Conversion to SR		Small numbers; Power not shown
			<2 h	Placebo 7/32, amiodarone 11/32, flecainide 20/34	
			>2 and <8 h	Placebo 18/32, amiodarone 19/32, flecainide 23/34	
Boriani *et al.*[96]	417 patients with recent onset AF (≤7 days), placebo versus amiodarone iv, flecainide po, propafenone iv or propafenone po	Cohort	Conversion to SR	As a percentage	
			At 1 h	Placebo 9, amiodarone 6, flecainide 13	
			At 3 h	Placebo 18, amiodarone 25, flecainide 57	
			At 8 h	Placebo 37, amiodarone 57, flecainide 75	
Martinez-Marcos *et al.*[93]	150 patients with acute onset AF (≤48 h). Amiodarone iv versus flecainide iv or propafenone iv	Randomized single-blind trial	Conversion to SR	As a percentage	
			At 1 h	Amiodarone 14, flecainide 29	
			At 8 h	Amiodarone 42, flecainide 82	
			At 12 h	Amiodarone 64, flecainide 90	

AF, atrial fibrillation; SR, sinus rhythm; iv, intravenous; po, *per os*.

Table 2 Relapse rates for different antiarrhythmic drugs reported in the literature[a]

	Mean relapse rate (range)	Studies (*n*)
No drug	69% (44–85)	10
Quinidine	59% (46–89)	11
Disopyramide	51% (46–56)	3
Propafenone	61% (54–70)	3
Flecainide	38% (19–51)	3
Sotalol	58% (51–63)	3
Amiodarone	47% (17–64)	4

[a]Minimum 6-months follow-up.
Adapted from Levy *et al.*[108]

Table 3 Ventricular proarrythmia risk factors for class 1C antiarrhythmic drugs

Risk factors
Wide QRS (>120 ms), Brugada ECG sign
Low LVEF, CHF
Structural heart disease, CAD
High rate (use-dependent effect)
High dose
Hypokalaemia
Severe renal failure (creatinine clearance ≤ 35 mL/min/1.73 m^2)
Excessive QRS increase (>150% from baseline)

CAD, coronary artery disease; CHF, chronic heart failure; LVEF, left ventricular ejection fraction; ECG, electrocardiogram.

quality of the studies differed markedly, and follow-up was mostly relatively short. Despite this, the conclusions are still valid; flecainide appears to be safe for patients with supraventricular arrhythmias without detectable heart disease, and it may contribute to suppression of AF- or SVT-related symptoms. The author concluded that the recommendation to perform intensive diagnostic tests to exclude associated cardiovascular disease, before initiating and during flecainide treatment, is valid.[111]

Mortality attributable to flecainide in the meta-analysis was lower than expected in the general population (total mortality: 0.166%; mortality rate per 100 patient years: 0.397). Compared with historical controls, the patient population of an AF study at Duke University (Durham, NC, USA) was much smaller, although it contained a significant proportion of patients with extensive underlying heart disease.[112] There was no evidence of increased or lower proarrhythmia events with flecainide compared with the compiled control drugs.

Information for first-time hospitalizations for AF between 1995 and 2004 was drawn from a nationwide registry in Denmark.[113] Within this unselected cohort ($n = 151\,500$) there was no association between antiarrhythmic treatment (flecainide, propafenone, sotalol, or amiodarone) and any increased risk of death and demonstrated that appropriate selection of patients for AAD therapy did not increase mortality as suggested in other trials such as CAST. Annualized mortality rates (as per year per 100 person-years) were lower with class IC agents (flecainide: 2.54; propafenone: 4.25; sotalol: 5.29; and amiodarone: 7.42), and few deaths were observed within 30 days of starting AADs, when proarrhythmic drug effects are most likely. This study was limited by its retrospective non-randomized nature, but the results are nonetheless promising.

In a study evaluating the cardiac safety of 200 mg flecainide acetate controlled-release formulation for the prevention of PAF, 4 of 227 patients had a maximum QRS value >100 ms under treatment. Bradycardia (13.2%; $n = 17/129$) and ventricular extrasystoles (10.6%; $n = 11/104$) were the most frequently identified proarrhythmic effects. Atrioventricular block (4.0%; $n = 9/227$), supraventricular tachycardia (2.2%; $n = 5/227$), bundle branch block (1.8%; $n = 4/227$), and AF (1.3%; $n = 3/227$) were the most frequent drug-related cardiac adverse events.[114] In this study, however, there was no comparison with controls. It was concluded that the cardiac adverse event rate was 'consistent with data from the literature for patients with supraventricular tachyarrhythmia'. The observation that QRS widening is the main cause of flecainide-related adverse effects suggests that controlled-release formulations may be safer than standard preparations.

The place of flecainide in atrial fibrillation

Flecainide is one of the first-line treatment recommendations for maintaining SR following cardioversion in the current guidelines.[3,4] These guidelines advise that patients with recurrent PAF may benefit from rhythm control with flecainide, particularly younger age groups with normal cardiac function. In the acute setting, flecainide is recommended for pharmacological cardioversion of PAF of no more than 7 days' duration, and there is also strong evidence supporting the use of flecainide prior to electrical cardioversion. One study found pre-cardioversion flecainide use resulted in more successful first shocks in comparison with placebo (65 vs. 30%, respectively; $P = 0.04$).[115] Another study concluded that 'Intravenous flecainide reduces atrial defibrillation threshold in patients treated with low-energy internal atrial cardioversion which results in lower shock-induced discomfort. Additionally, flecainide may increase the procedure success rate in patients with chronic persistent atrial fibrillation'.[116]

The case for early treatment

It is easy to underestimate the impact of AF. By the time AF is confirmed, remodelling will already be underway; the first-documented episode may be only one of a series of unrecognized episodes.[10,14,117] If left untreated, the condition will become chronic through its own self-perpetuating mechanism.[15] Clinicians who see many AF patients are more aware of the impact of AF on patients' wellbeing; frequently AF patients do not fully appreciate the extent to which their QOL has been diminished until SR has been restored.

Atrial fibrillation is widely accepted as a condition of the elderly; however, around half of patients presenting with PAF are <60 years old. Nevertheless, current treatment guidelines are based on large randomized controlled clinical trials, such as the AFFIRM,

RACE, and STAF studies, which had mean patient ages of 70, 68, and 66 years, respectively.[21–23] In these studies, patients also had established persistent AF at inclusion and most had other cardiovascular risk factors, restricting the choice of therapy. There is an increasing view among clinicians that younger, healthier patients should be restored to and maintained in SR through aggressive treatment at the very first sign of the illness.[6] In this population, maintaining SR is vital so as to interrupt the process of atrial remodelling, and to improve QOL[101,118,119] and long-term survival.[8] A recent position paper proposed a tightening of the treatment guidelines for newly discovered AF to recommend early treatment with AAD therapy to restore the patient to SR.[6]

When selecting the appropriate AAD, the treatment should be tailored to each patient; the often complex presentation of AF makes this a challenging task. Flecainide has been on the market for 27 years, and its capacity to reduce AF symptoms and provide long-term restoration of SR has been well documented.[92,93,102–108] However, the increased mortality reported in CAST still deters many clinicians from using a class 1C AAD. This denies many new AF patients a valuable treatment option. The increased mortality seen in patients treated with flecainide in CAST is now viewed as having been caused by proarrhythmic events in elderly patients with significant pre-existing cardiovascular comorbidity.[78] Important treatment decisions should not be based on this single study; there is now a body of evidence supporting the use of flecainide, clearly demonstrating that in AF patients without significant LV disease or CAD, the drug has a favourable safety profile with a low incidence of proarrhythmic and other cardiac and non-cardiac adverse events. As a result of this evidence, flecainide is now recommended as one of the first-line treatment options for restoring and maintaining SR in patients with AF under the current ACC/AHA/ESC guidelines and the updated ESC guidelines.

Conclusions

Atrial fibrillation is a 'ticking bomb'. The increasing prevalence of AF may result in an epidemic of associated heart disease with a major impact on patients QOL. Early detection and aggressive treatment can help break the vicious circle where 'AF begets AF'.

Over the last 25 years, flecainide has been used extensively worldwide. The abundance of experience and knowledge gathered during this period supports flecainide as a safe and effective option for achieving and maintaining SR in younger patients without co-existing structural heart disease. Furthermore, our increased understanding of the pathophysiological mechanisms underlying AF provides a strong rationale for early treatment with flecainide to prevent long-term complications.

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