Use of Flecainide for the Treatment of Atrial Fibrillation

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Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with substantial morbidity and impairment of quality of life. Restoration and maintenance of normal sinus rhythm is a desirable goal for many patients with AF; however, this strategy is limited by the relatively small number of antiarrhythmic drugs (AADs) available for AF rhythm control. Although it is recommended in current medical guidelines as first-line therapy for patients without structural heart disease, the use of flecainide has been curtailed since the completion of the Cardiac Arrhythmia Suppression Trial. In clinical trials and real-world use, flecainide has proven to be more effective than other AADs for the acute termination of recent onset AF. Flecainide is also moderately effective and, with the exception of amiodarone, equivalent to other AADs for the chronic suppression of paroxysmal and persistent AF. In patients without structural heart disease, flecainide has been demonstrated to be safe and well tolerated relative to other AADs. Despite this favorable profile, flecainide is underutilized, likely due to a perceived risk of ventricular proarrhythmia, a concern that has not been borne out in patients without underlying structural heart disease. Guidelines for administration and use of flecainide are summarized in this review. **(Am J Cardiol 2020;125:1123−1133)**

Atrial fibrillation (AF) is the most common sustained arrhythmia and one which is associated with substantial morbidity and symptoms which negatively impact quality of life. Rhythm control is, therefore, a desirable goal for many patients with recurrent AF. Moreover, the recent availability of wearable, handheld, and implantable ECG monitoring devices with the capability to automatically detect AF[1−6] will generate continued growth in the numbers of patients requiring treatment for AF. However, there are relatively few antiarrhythmic drugs (AADs) currently available for AF rhythm control. Current medical guidelines include flecainide as a first-line agent for the conversion and suppression of intermittent episodes of AF in patients without structural heart disease.[7,8] Although the safety of flecainide in patients without structural heart disease is well established and has been comprehensively reviewed,[9] its use continues to be limited,[10] primarily owing to concerns about the risk of ventricular proarrhythmia following the results of the Cardiac Arrhythmia Suppression Trial (CAST).[11] The purpose of this report is to review the efficacy and safety of flecainide for the treatment of patients with AF, compare it with other approved AADs, and propose recommendations for its use, nearly 3 decades after the results of CAST were published.

Background

Cardiac Electrophysiology

Flecainide is an antiarrhythmic agent with membrane stabilizing activity. It is categorized as a Vaughn-Williams Class IC agent based upon its properties of markedly slowing cardiac conduction with a minimal effect on ventricular repolarization.[12,13] Flecainide's primary electrophysiological actions are due to its voltage and use-dependent block of cardiac voltage-gated sodium channels, causing inhibition of the transient peak inward sodium current (I_{Na}).[14] The combination of its use-dependent (rate-dependent) sodium channel block and its slow kinetics result in a greater reduction in myocardial tissue excitability during tachyarrhythmias. In addition to inhibiting the transient peak I_{Na}, flecainide also inhibits the slow inactivating component of I_{Na}, referred to as late I_{Na},[15] the rapid component of the delayed rectifier potassium (K^+) current (I_{Kr}), and the time-dependent transient outward current I_{to}.[16,17] In addition, flecainide inhibits the ryanodine receptor, RyR2.[18]

The precise electrophysiological mechanism(s) responsible for flecainide's conversion and suppression of AF is unknown. Based upon results in human studies[19,20] and experimental animal studies,[21−25] the electrophysiological properties likely to contribute to flecainide's antiatrial fibrillatory effects include: (1) rate-dependent prolongation of atrial refractoriness, (2) greater prolongation of atrial refractory period than action potential duration (postrepolarization refractoriness), (3) decrease in excitability, and (4) suppression of spontaneous diastolic SR Ca^{2+} release.

The precise mechanism(s) responsible for flecainide's ventricular proarrhythmic potential is also unknown. However, the ionic basis can be explained by exaggerated effects of inhibition of peak I_{Na} in partially depolarized (eg, ischemic)

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myocardium, rapid rates (use-dependence), and the slow kinetics of dissociation for the sodium channel. Based upon experiments in animal models, ventricular proarrhythmia attributed to sodium channel blocking drugs are caused by marked rate-dependent slowing of conduction in ischemic and infarcted myocardium, promoting heterogeneity of conduction and facilitating initiation of reentrant wavefront activity.[26] In rabbit and canine models of myocardial infarction (MI), programmed electrical stimulation in combination with flecainide administration enabled easily inducible[27,28] and spontaneous[28] reentrant ventricular tachycardia. These experimental findings of markedly increased susceptibility to ventricular proarrhythmia with flecainide administration in the setting of MI are consistent with the findings of the CAST (see section on FDA labeling and the CAST).

Ventricular proarrhythmia with flecainide is rarely manifested as torsade de pointes, as is seen with QT-prolonging drugs, because the drug's inhibition of I_{KR} is relatively weak and countered by its inhibition of peak and late sodium current.[29] Unlike QT-prolonging drugs and torsade de pointes, sodium channel blocking drugs do not have a unique ECG signature that enables a specific diagnosis of drug-related ventricular arrhythmias. Ventricular tachyarrhythmias with ECG morphologies characterized by markedly widened or sinusoidal QRS complexes may occur in the presence of flecainide-induced sodium channel toxicity, and also in the absence of flecainide but the presence of hyperkalemia, ischemia, or severe left ventricular dysfunction. Flecainide toxicity due to high plasma concentrations can also masquerade as ventricular proarrhythmia, because of markedly widened QRS complex durations during supraventricular rhythms such as AF or flutter, as illustrated in a recent case report.[30] The differential diagnosis of sodium channel toxicity can be clinically useful because, in addition to withdrawal of flecainide, treatment may include hypertonic sodium bicarbonate, lidocaine, cardiac pacing, and mechanical hemodynamic support if needed.[31]

Flecainide prolongs the sinus node recovery time in some patients with underlying sinus node dysfunction[32,33] which may be the mechanism responsible for postconversion sinus pauses occasionally observed in patients following the conversion of AF to sinus rhythm (SR). Flecainide also increases pacing thresholds,[33] but this effect has not proven to be of clinical significance with implanted cardiac pacemakers because programmed output settings routinely incorporate a safety margin.

The effects of flecainide on the 12-lead electrocardiogram are primarily attributed to its marked effects on intra-atrial, AV node, His-Purkinje, and intraventricular conduction.[34,35] Prolongation of the PR and QRS interval durations are concentration-dependent and readily apparent, ranging from 17% to 29% for PR and 11% to 27% for QRS in reported studies.[35] The vast majority of the prolongation of the QTc interval (ranging from 1% to 5%) is a consequence of the increase in QRS interval duration.[35–37]

Hemodynamic Effects

Flecainide has negative inotropic properties. Intravenous (IV) administration of flecainide, even in patients without structural heart disease hearts, can cause hypotension,[38] and/or reduced stroke volume and cardiac output.[39] In patients with coronary artery disease, IV flecainide has been reported to reduce stroke volume, cardiac output, and ejection fraction; and increase pulmonary capillary wedge pressure, especially in those with concomitant left ventricular (LV) dysfunction.[40,41] The hemodynamic effects of flecainide with chronic oral administration are dependent on underlying LV function. In patients without structural heart disease or with minimal LV functional abnormalities, no effect on blood pressure or ejection fraction has been found.[37,42,43] However, in a study of patients with LV dysfunction, new or worsened heart failure was observed in 21% of patients, but only in those with a baseline ejection fraction of <30%.[44]

Pharmacology

The absorption of orally administered flecainide acetate is slow with peak plasma drug levels (C_{max}) reached at an average of 3 hours (T_{max} from 1 to 6 hours), but nearly complete (90% to 95% bioavailability).[45] Flecainide does not undergo first past hepatic metabolism. Therapeutic flecainide plasma levels with a total daily dose of 200 to 500 mg range from 200 to 1,000 ng/ml,[36] and within this range there is a linear relation between plasma level and dose.[45] Flecainide undergoes hepatic oxidative metabolism via cytochrome CYP2D6 and CYP1A2. The mean elimination half-life of oral flecainide is about 13 hours (range 7 to 22 hours), and is unaffected by dose.[45] Both flecainide and its major inactive metabolites are primarily excreted in the urine.[45] The pharmacokinetics of IV flecainide is notable for a rapid initial distribution phase of about 5 minutes, and elimination half-life of 7 to 15 hours (mean 11 hours).[46]

Flecainide Administration and AF Indications for Use

Flecainide acetate is available globally in oral formulation; its IV formulation is available in many countries but not the United States. Oral and IV flecainide have a Class 1A designation for the acute pharmacologic conversion of recent AF. IV flecainide, where available, is commonly used in emergency departments for the acute termination of AF. Intermittent self-administration of oral flecainide for the acute termination of recent-onset AF, termed "pill-in-a-pocket," has a Class IIA designation. Chronic administration of oral flecainide has a Class IA recommendation in current guidelines from the United States[7] and EU[8] for the suppression of AF in patients without structural heart disease with recurrent paroxysmal or persistent AF.

FDA Labeling and the CAST

Flecainide acetate (Tambocor) was initially approved in 1985 for the treatment of supraventricular and ventricular tachyarrhythmias. In 1987, it was included in a randomized clinical study of 4 AADs and placebo, the CAST.[47] The CAST sought to test the hypothesis that the suppression of premature ventricular contractions (PVCs) would prevent sudden cardiac death in patients with frequent ventricular ectopy and reduced ejection fraction following a recent MI. However, 2 of the AADs tested, encainide and flecainide, were found to increase mortality compared with placebo in an interim analysis in 1989, and their use in the trial was halted.[11] It is notable that the actual mortality rate with flecainide was 4.3%, lower than the assumed placebo mortality rate of 5% used to design the

study. The majority of excess deaths were due to ventricular tachyarrhythmias or asystole, and the second most common cause was MI with shock. The mortality rate was relatively linear over the mean of 10 months of follow-up. Death attributed to proarrhythmia occurred despite suppression of PVCs on ambulatory monitoring. The total number of arrhythmias and myocardial ischemic events in the active drug and control groups were similar, but in the active drug groups these events were 5 times more lethal. The relative mortality risk was also 5 times higher in patients experiencing non-Q wave MI compared with Q wave MI during follow-up.[48] Therefore, it is postulated that in the CAST population, lethal acute ischemia was the proarrhythmic mechanism responsible for both the deaths due to MIs and the triggering of ventricular tachyarrhythmias.[49,50] There is also speculation that the negative inotropic properties of encainide and flecainide contributed to the lethality of the MIs and ventricular tachyarrhythmias. However, although there was a slightly higher heart failure event rate in patients assigned to encainide and flecainide, this did not translate to a higher mortality due to heart failure. In fact, no death associated with flecainide was attributed directly to progressive heart failure. Because of the CAST findings of proarrhythmia, the FDA label was amended to include a black box warning. Although the CAST patient population was comprised only of post-MI patients with reduced ejection fraction, the FDA determined that its use be contraindicated in patients with structural heart disease of any etiology.

Other Indications for Use

Flecainide is indicated for patients with atrial flutter, paroxysmal supraventricular tachycardia, and the prevention of documented life-threatening ventricular arrhythmias. Flecainide may be particularly effective for patients with catecholaminergic polymorphic ventricular tachycardia, presumably due to its inhibitory action on RyR2 channels, and is a subject of an ongoing clinical trial.[18,51] It has also been used off-label in a small cohort of patients with PVC-induced cardiomyopathy, but without ischemic heart disease, resulting in a reduction in PVCs and improvement in ejection fraction with no evidence of proarrhythmia after a mean of 3.8 years of treatment.[52]

Efficacy of Flecainide for the Treatment of AF

Acute Conversion of AF

Flecainide administration is highly effective for the conversion of AF to SR.[53,54] The most objective method by which to evaluate pharmacologic conversion rates is to randomize patients to drug or placebo and use a prespecified end point time to control for spontaneous conversion rates.[55] Results from 4 such trials with flecainide are depicted in the histograms of Figure 1.[56–59] Overall, the conversion rate with flecainide ranged from 57% to 80%, higher than the conversion rate with placebo which ranged from 14% to 37%. The study with the 8-hour end point[59] utilized oral flecainide, whereas the other 3 studies[56–58] utilized IV flecainide. The lower conversion rates observed in 2 studies[56,57] are likely due to the shorter end point times at which conversion efficacy was assessed. In a meta-analysis of 6 studies,[38] with a conversion end point time of 2 hours, IV flecainide administration was associated with a 69% conversion rate compared with 16% with placebo or verapamil.

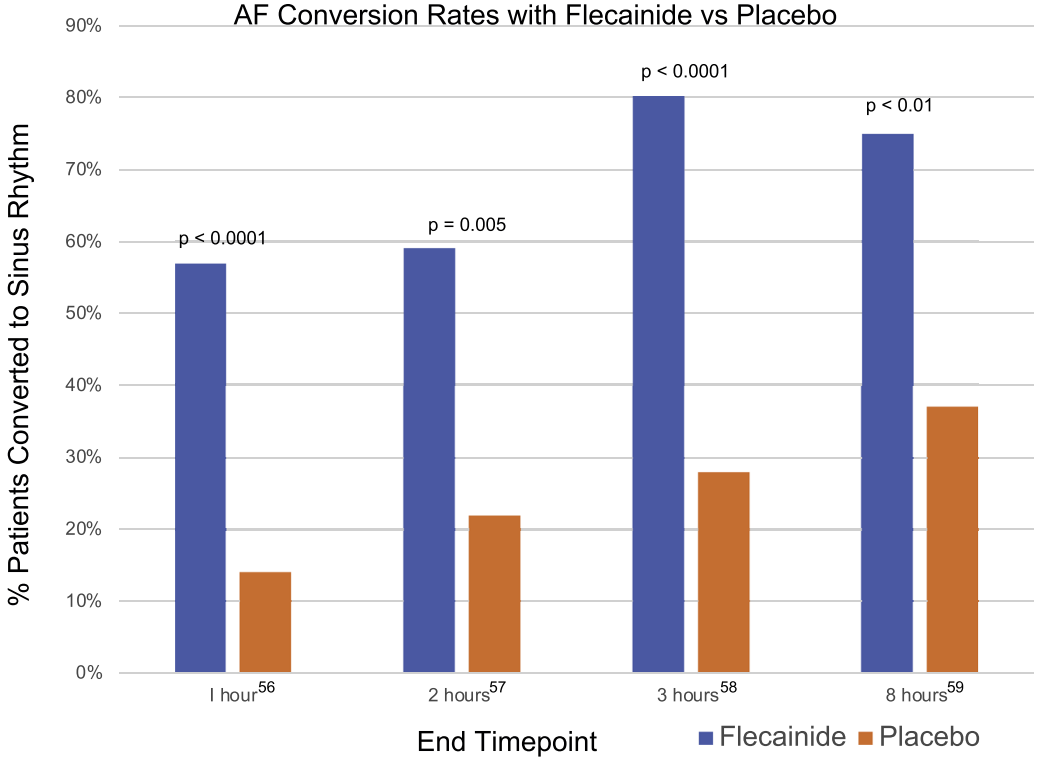

Figure 1. Acute AF conversion rates at 1 hour,[56] 2 hours,[57] 3 hours,[58] and 8 hours[59] after administration of flecainide or placebo.

Acute Conversion of AF With Flecainide Compared With Other Antiarrhythmic Agents

The other Class IC antiarrhythmic agent approved for acute conversion of AF is propafenone, whose use is also restricted to patients without structural heart disease. Figure 2 depicts the conversion rates for flecainide and propafenone in 5 randomized controlled studies comparing the agents directly.[58,60–63] In each study, the conversion rate with flecainide (range 50% to 90%) was higher than with propafenone (range 25% to 72%).

Other antiarrhythmic agents recommended in medical guidelines for AF conversion are all categorized as having predominantly Class III effects. These include 3 IV agents: amiodarone, ibutilide, and vernakalant (not available in the United States); and oral dofetilide (not available in Europe). Beta-blockers, calcium channel blockers, and digoxin, while often given concomitantly for rate control, are not recommended alone for rhythm control therapy as they have not been shown to result in AF conversion compared with placebo.[8] Of the AADs recommended for acute conversion of AF to SR, amiodarone is the most commonly used in the United States despite the fact that it is not approved for the treatment of supraventricular arrhythmias,[64] and conversion of AF and SR with the drug is delayed due to its pharmacokinetics. Based upon a meta-analysis of studies comparing IV amiodarone with placebo and/or Class IC agents,[64] unlike flecainide, the AF conversion rate with IV amiodarone administration was similar to placebo at 1 to 2 hours after administration, higher than placebo but lower than flecainide at 6 to 8 hours after administration, and only at 24 hours was the conversion rate with amiodarone comparable with the rates attained at 6 to 8 hours with flecainide.[64] Shown in Figure 3 are conversion rates over time from 2 studies evaluating IV amiodarone and oral[57] or IV flecainide.[63] In an emergency room propensity score case-matched study comparing Class IC agents with amiodarone, higher AF conversion rates (73% vs 53%, p <0.05) combined with equivalent adverse event rates resulted in a lower hospital admission rate with Class IC drugs (27% vs 52%, p <0.05).[65]

A meta-analysis of randomized studies found the overall AF conversion rate within 2 hours to be higher with flecainide (66%) compared with the AADs amiodarone, propafenone, sotalol, procainamide, and ibutilide (46%).[38] Randomized studies directly comparing flecainide AF conversion rates with dofetilide and vernakalant are not available; however, in studies with a placebo comparator, the conversion rates were lower than reported for flecainide.[66] Thus, acute conversion of recent onset AF is higher with flecainide than any other antiarrhythmic agent.

Pill-in-the-Pocket Approach

Because flecainide and propafenone have been shown to be effective for acute conversion of AF when administered as an oral loading dose,[54,62,67] their use has been extended to intermittent self-administration by the patient, referred to as "pill-in-the-pocket" (PiP). This treatment strategy has been employed for selected patients who are able to reliably self-identify symptomatic episodes of AF or are able to obtain confirmation from a wearable, implantable, or portable ECG monitoring device. Patients generally have an initial AF episode treated under medical supervision and, if conversion is successful and without major adverse events, the treatment is prescribed for home use. Because patients are prescreened for efficacy and safety and are able to self-treat soon after AF onset, the conversion rate can be high and the overall duration of AF relatively short. In 1 study,[68] initial acute conversion in the emergency room was successful and without adverse events in 78% of patients treated. Of 165 patients subsequently self-treating 618 episodes of AF with flecainide or

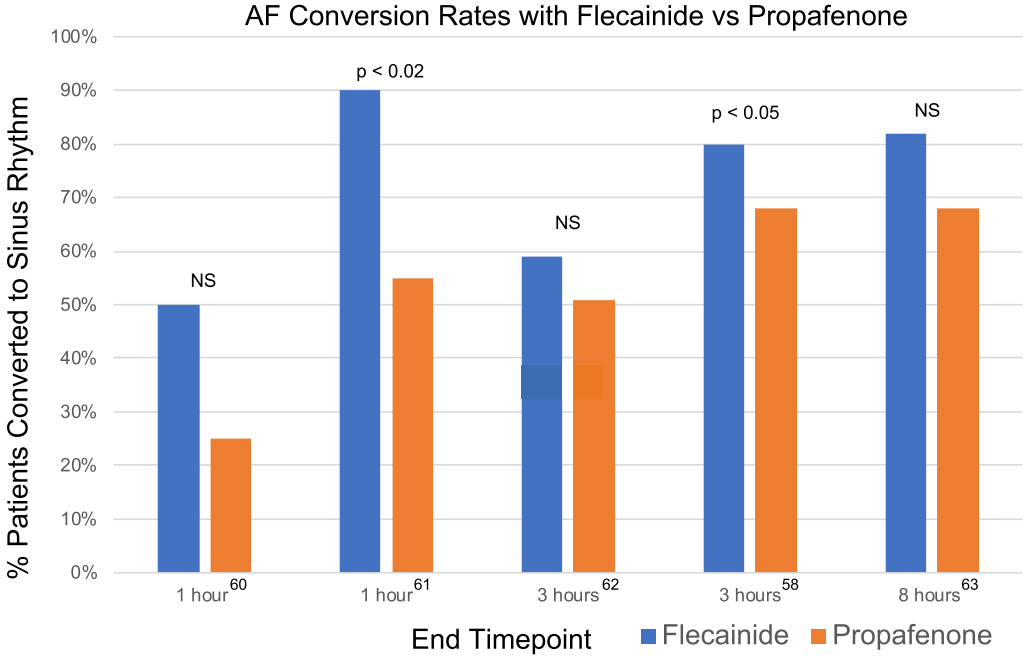

Figure 2. Acute AF conversion rates at 1 hour,[60,61] 3 hours,[58,62] and 8 hours[63] after administration of flecainide or propafenone. Note that oral agents were administered in the study by Capucci et al.[62]

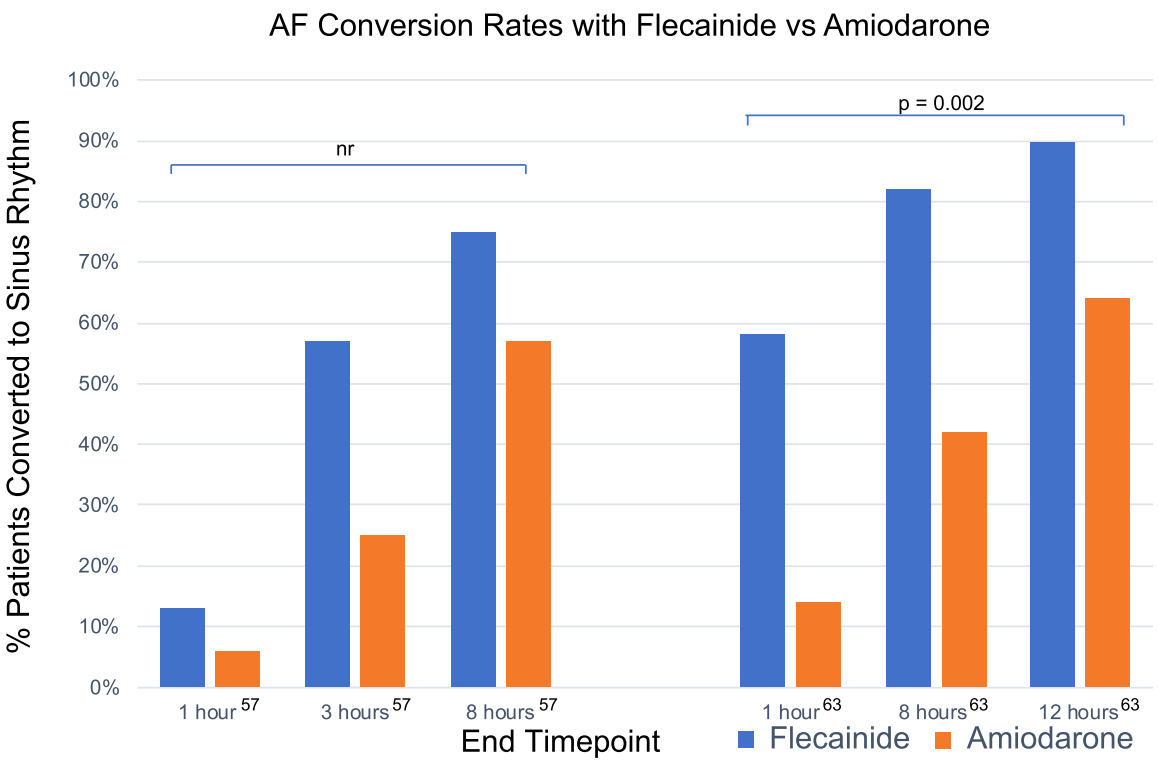

Figure 3. Acute AF conversion rates at various time points after administration of po flecainide or IV amiodarone[57] (left bars) and IV flecainide or IV amiodarone[63] (right bars). nr = not reported.

propafenone, the conversion rate was 94% and the mean AF duration was 113 ± 84 minutes. In 84% of the 165 patients, self-treatment was successful for all AF recurrences. In a similar study,[69] 70% of patients were initially treated successfully and safely, and those 30 patients subsequently had 159 episodes of AF, 97% of which were successfully self-treated. This treatment strategy significantly reduced the number of emergency room visits,[68,69] the need for electrical cardioversion,[69] and the need for hospitalization[68] compared with a similar time period before initiating the PiP approach.

Chronic Suppression of AF With Flecainide

The primary role of chronic therapy with flecainide and other AADs is to delay the time to AF recurrence and reduce AF burden. It is difficult to determine actual AF recurrence rates from reported studies of chronic suppression because they are based upon routine intermittent ECG monitoring and documented symptomatic events. Asymptomatic episodes occurring outside of ECG monitoring periods and symptomatic episodes without ECG documentation are not usually reflected in the reported results. Chronic oral flecainide administration has been shown to reduce the incidence of AF recurrence and prolong the interval between episodes in patients with paroxysmal and persistent AF in small placebo-controlled studies,[70–73] and 65% of patients were AF-free at 9 months in a larger uncontrolled study.[74]

Chronic Suppression of AF With Flecainide Compared With Other AADs

Large retrospective studies and meta-analyses of AAD therapy that report 1-year AF recurrence rates range from 44% to 67%.[75–78] The efficacy of flecainide was found to be similar to other AADs,[75,77] or similar with the exception of somewhat greater efficacy with amiodarone.[76,78] Hospitalization rates for AF following AAD prescriptions for a new diagnosis of AF or atrial flutter have been analyzed using health utilization data. In the TREAT-AF study, which employed propensity score matching, not only were hospitalization rates for AF or atrial flutter found to be lower with Class IC drugs, but also for cardiovascular disease, heart failure, and ischemic stroke.[79] Another analysis using claims data[80] found higher AF hospitalization rates with dronedarone and lower AF hospitalization rates with amiodarone, but no difference between sotalol and Class IC AADs. Thus, with the exception of amiodarone, the long-term efficacy of flecainide is comparable with other approved AADs.

Prophylactic Flecainide Post Cardiac Ablation

AF recurrence is common in the 3-month atrial healing period immediately following catheter ablation, referred to as the blanking period.[81] Prophylactic AAD therapy during the blanking period has been found to be an effective strategy even in previously drug refractory patients. Several randomized trials which have included flecainide have shown that the incidence of recurrent AF is modestly reduced on AADs (3% to 52%) compared with placebo (22% to 59%).[82–84]

Safety of Flecainide in Patients With AF

Major Safety Issues With Flecainide

The 2.5-fold excess mortality due to proarrhythmic effects associated with the use of encainide and flecainide in the CAST occurred in a highly selected population of patients

with previous MI, frequent ventricular ectopy, and depressed LV ejection fraction.[11] Despite the fact that the CAST was carried out in a high-risk cohort of patients with advanced structural heart disease, potential safety concerns about the risk for ventricular proarrhythmia in other populations has persisted. Flecainide-induced proarrhythmia manifesting as ventricular tachycardia can be either monomorphic or polymorphic, but very rarely has the morphologic characteristics of torsade de pointes, as discussed in the section on flecainide electrophysiology. Despite these concerns, the safety of flecainide in patients without structural heart disease is now well established.

Three additional arrhythmia-related safety issues have been reported to be associated with the use of flecainide in patients with AF. First, there is the potential for AF to be converted to atrial flutter as a result of the conduction slowing effects of flecainide.[85] When this occurs, the atrial (flutter) rate may be slowed enough to permit one-to-one AV conduction, resulting in a rapid ventricular rate. In patients with healthy AV node function, the concomitant administration of a β blocker or nondihydropyridine calcium channel blocker markedly reduces the likelihood of this adverse event. Second, is the possibility of a prolonged sinus pause immediately following successful conversion of AF to SR.[86] These offset pauses occur primarily in patients with underlying sinus node dysfunction. Third, flecainide, like many other sodium channel blocking drugs, may unmask the ECG pattern of underlying Brugada syndrome, leading to ventricular tachycardia and, thereby, a risk for sudden cardiac death.

Another major safety issue associated with administration of flecainide is related to its potential for adverse hemodynamic effects resulting from the negative inotropic effect of the drug. Hypotension can be observed following IV administration regardless of underlying LV function. Worsening heart failure has been observed in patients with underlying LV dysfunction receiving chronic oral therapy, which is why the use of flecainide is contraindicated in patients with LV dysfunction or heart failure. Minor adverse effects associated with flecainide administration include dizziness, visual disturbances, paresthesias, headache, dyspnea, and nausea.

Analyses of Mortality

Following the results of the CAST, numerous flecainide safety analyses were performed for patients with supraventricular tachyarrhythmias. A meta-analysis of 91 randomized controlled trials of AAD therapy for short-term AF rhythm control, with a mean follow-up of 46 days, found 99% survival in both drug and control groups.[87] There was no evidence of an adverse mortality effect with any AAD including flecainide. In contrast, analyses of chronic suppression of AF have found differing all-cause mortality rates among AADs. In the Swedish Patient registry of patients receiving AADs with propensity scored-matched controls, followed for a mean of 3.5 years, a significantly higher total mortality rate was observed in patients treated with amiodarone compared with sotalol, and a significantly lower total mortality rate with chronic flecainide therapy compared with sotalol.[88] This analysis also found a higher composite arrhythmic end point rate with amiodarone compared with sotalol, and an equivalent arrhythmic end point rate with flecainide compared with sotalol. A meta-analysis that compared 1-year mortality rates in 59 randomized controlled trials comprised of AADs for chronic AF suppression found that none resulted in a mortality benefit and that only Class IA agents and sotalol were associated with an increase in mortality compared with controls.[78] The AFFIRM trial randomized 4,060 patients to rate or rhythm control drug treatment strategies for AF using mortality as the primary end point.[89] Although no difference in mortality was observed between the rate versus rhythm control arms, a propensity score-matched subset analysis of mortality with individual AADs provided further insights.[90] There was no difference in mortality in the minority of patients randomized to rhythm control and receiving flecainide (8%) compared with the rate control arm. However, a majority of patients randomized to rhythm control received amiodarone (63%), resulting in a trend toward higher total mortality, and a significantly higher incidence of noncardiovascular mortality compared with the rate control arm. Furthermore, a separate AFFIRM analysis found that the (nonsignificant) excess mortality in the rhythm control arm was entirely noncardiovascular in etiology, and primarily pulmonary and cancer-related, which are disease states most closely associated with chronic amiodarone use.[91] Since the majority of patients in the rhythm control arm received amiodarone, it is plausible that the excess noncardiovascular mortality associated with amiodarone use was primarily responsible for the overall lack of difference in mortality between rate and rhythm strategies in the AFFIRM. Mortality was also compared in a propensity-matched cohort analysis of patients with LV hypertrophy treated for persistent AF with amiodarone and nonamiodarone AADs.[92] A trend toward higher mortality was found with amiodarone compared with nonamiodarone drugs, and a significantly higher mortality was found with amiodarone compared with the subset of patients receiving Class 1C agents. Overall, these analyses suggest that acute and chronic therapy with flecainide does not confer a mortality benefit or risk compared with controls in patients with AF, but that flecainide may confer a lower mortality risk compared with sotalol and amiodarone. Furthermore, there appears to be a higher risk of death with chronic amiodarone therapy compared with controls.

Analyses of Ventricular Proarrhythmic Effects During Acute Administration

Most of safety analyses addressing proarrhythmia combine acute and chronic studies of flecainide administration and also combine all types of arrhythmia-related adverse events. To consider the specific concern of proarrhythmia due to ventricular tachyarrhythmias in the setting of acute administration for AF conversion, individual studies were reviewed. Combining the results from the 4 randomized controlled studies of acute AF conversion with flecainide, shown in Figure 1,[56–59] 1 event in 292 patients treated with flecainide and 1 event in 254 patients treated with placebo was considered to be ventricular proarrhythmia. Combining the results from 3 studies using the PiP approach with either flecainide or propafenone, there was no evidence of ventricular proarrhythmia in the 433 patients treated in-hospital for their initial episode or any of the 990 episodes in 274 patients treated out-of-hospital.[68,69,93]

Analyses of Total Arrhythmia-Related Adverse Events

A large meta-analysis of 122 studies[94] that included both acute and chronic treatment with flecainide for supraventricular tachyarrhythmias found that the incidence of all arrhythmia-related adverse events with flecainide was significantly lower than that of active comparators and placebo controls (2.5% vs 3.2%, p <0.001). A more recent meta-analysis of studies on acute AF conversion[38] found that the incidence of arrhythmia-related adverse events was similar for IV flecainide, placebo, amiodarone, propafenone, sotalol, dofetilide, and ibutilide. The same study reported that the risk of hypotension with IV flecainide was statistically significantly higher than with placebo but not higher than with other AADs.

Analyses of Total Adverse Events

In a propensity score case-matched study of acute AF conversion, the total adverse event rate with IV Class IC drugs and amiodarone was found to be similar (3.4% and 3.9%, respectively), and the most common event was minor hypotension.[65] In a meta-analysis of 122 studies of acute and chronic AAD administration, the total rate of adverse cardiac events was 5.6% for flecainide compared with 5.8% for placebo and active control groups combined.[94] The incidence of major adverse events with acute and chronic administration of flecainide in the currently indicated treatment population (ie, no structural heart disease), is summarized in Table 1. These studies support the conclusion that the risk of major adverse events with flecainide, including mortality, ventricular proarrhythmia, and other arrhythmia-related events, is similar to other AADs used to treat AF.

Recommendations for Flecainide Administration and Management

There are a number of important benefits to early conversion and prevention of recurrent AF. The concept that "AF begets AF," demonstrated in animal studies,[95] is attributed to atrial mechanical dysfunction and structural and electrical remodeling.[26] A greater AF burden is associated with a higher risk of cardiovascular complications, progression of paroxysmal AF to chronic AF, and a higher incidence of stroke.[96] Additionally, it is generally accepted that anticoagulation is indicated when AF exceeds 48 hours in duration. Early conversion is an advantage not only to patients but to the healthcare system as well by reducing resource utilization and hospital admission rates.

The choice among rhythm control strategies is a topic that has been discussed extensively elsewhere.[55,97–102] In general, treatment should be individualized, primarily based upon symptoms, quality of life, and patient preference. In patients with heart failure, there is clear evidence of combined mortality and rehospitalization benefit with cardiac ablation.[100,103] Importantly, the use of cardiac ablation and AADs are not mutually exclusive. For instance, in young patients who are good candidates for both flecainide and cardiac ablation, acute conversion and a trial of chronic suppression using flecainide has utility as initial therapy while evaluating AF frequency and symptoms, during the postablation blanking period,[82–84,104] and for postablation recurrences.

For patients with AF and minimal or no structural heart disease, flecainide has clear clinical utility for the early termination of AF and for the prevention of AF recurrences. Both IV and oral flecainide have demonstrated the highest efficacy rates for acute pharmacologic conversion of recent-onset AF, with a safety profile comparable with or better than other agents. For selected patients, the PiP approach can, in addition to rapid conversion of AF, obviate the need for emergency room visits.[68,69,93] Current medical guidelines recommend the use of flecainide as a first-line agent for pharmacologic conversion of AF in patients without structural heart disease. Amiodarone is a second-line choice because of lower efficacy rates and delayed time to conversion, primarily for patients with structural heart disease.

For the prevention of AF recurrence in patients with paroxysmal or persistent AF and no or minimal structural heart disease, flecainide has demonstrated efficacy and safety equivalent to that of propafenone, sotalol, dronedarone, and dofetilide. Current guidelines[7] state that there is no clear preferred choice of AAD to use for this indication, but emphasize that amiodarone should be considered a second-line agent due to its greater long-term toxicity. Caution should be exercised in prescribing flecainide to patients with known sinus, AV node, or infranodal conduction delays, and flecainide should be avoided entirely in patients with myocardial ischemia or infarction, coronary artery disease, LV dysfunction, or congestive heart failure. The following of AF treatment guidelines by practitioners remain a significant issue. The ORBIT-AF study[105] sought to evaluate concordance with current guidelines in a registry of 176 sites in the United States. The guideline found to have the lowest concordance of only 44% stipulates that flecainide or propafenone should not be used in patients with coronary artery disease. The guideline with the next lowest concordance of

Table 1
Flecainide safety issues

Indication	Major adverse events	Relative incidence*
Acute conversion[38,56–59,68,69,91]	Sudden cardiac death, ventricular tachyarrhythmia	Rare
	1:1 atrial flutter	Unusual
	Bradyarrhythmia, sinus pause, heart block	Unusual
	Hypotension	Occasional (mostly with IV)
Chronic prevention[54,71,72,74,85,86]	Sudden cardiac death, ventricular tachyarrhythmia	Rare
	1:1 atrial flutter	Unusual
	Bradyarrhythmia, sinus pause, heart block	Unusual
	Worsened heart failure	Rare

* Rare <1%, Unusual 1% to <3%, Occasional 3% to <10%, Frequent ≥10%.

Table 2
Flecainide dosing and administration

Indication	Dose range	Comments
Acute conversion		
Oral	200-300 mg, single administration[7,8]	First treatment under medical supervision Anticipate maximum effect and conversion after 2-4 hours monitor BP, ECG
Intravenous	1.5-2 mg/kg, maximum 150 mg, infused over 10 min[8]	Anticipate maximum effect and conversion at end of infusion Monitor BP closely, ECG
Chronic prevention	50-200 mg bid	Start at 100 mg bid, adjust after 4 days. Monitor ECG, check QRS duration before dose escalation

65% stipulates that amiodarone should only be used as first-line therapy in patients with heart failure, LV hypertrophy, or LV dysfunction.

Recommendations for Dosing and Administration

Recommendations are summarized in Table 2. Blood pressure should be monitored due to the negative inotropic properties of the drug. Continuous ECG monitoring is needed to evaluate changes in QRS duration, the conversion of AF to atrial flutter with 1:1 AV conduction, and postconversion sinus pauses. For appropriately selected patients who have received an initial oral loading dose under monitored conditions in whom conversion is successful and there are no adverse events, flecainide can be safely prescribed for patient self-administration at the onset of recurrent AF.[68,69] For patients in whom the ability to self-diagnosis AF is questionable, it is recommended that the diagnosis be confirmed with a wearable, portable, or implanted ECG device.

For the chronic prevention of AF recurrence, it is not necessary to hospitalize the patient for initiation of therapy. However, it is important to obtain 12-lead ECGs at baseline, at steady state and before increasing the dosage. In addition, patients should have an echocardiogram to document the presence of normal LV function and exercise stress testing to rule out the presence of inducible myocardial ischemia before the initiation of chronic oral therapy. The most commonly used doses are 100 to 150 mg bid.[8] Flecainide is usually initiated at 100 mg bid, though a minority of patients will respond to doses as low as 50 mg BID. The dose may be escalated based on QRS duration prolongation of less than 50% over baseline after 4 days of administration.

Concomitant Therapy With Beta-Blocking Agents

The concomitant administration of beta-blocking therapy is recommended for both acute conversion and chronic AF suppression to reduce the potential for rapid AV node conduction should flecainide convert AF to atrial flutter.[7] However, β blockers should not be prescribed in patients with advanced sinus node dysfunction or abnormalities in AV node conduction. Beta blockers alone are rarely effective in the acute conversion of AF or the prevention of recurrence in patients without heart failure.[106]

Conclusions

Flecainide acetate is highly effective for the acute termination of recent onset AF and is moderately effective for the chronic suppression of AF. The drug has an excellent safety profile when administered to patients with minimal or no structural heart disease. Flecainide is more effective and safer than other AADs for the acute conversion of patients in AF. Despite its favorable safety and efficacy profile in patients with no or minimal structural heart disease, flecainide is underutilized due to misconceptions about the risk for ventricular proarrhythmia, a safety concern that has not been observed. Pharmacologic conversion of episodic AF with flecainide should be considered in eligible patients to accomplish rhythm control without chronic drug exposure and to avoid the necessity for electrical conversion. The ideal pharmacologic approach is one that appropriately selected patients can self-administer to terminate AF rapidly and safely. The PiP approach avoids the need for these patients to seek emergency care. With the recent availability of wearable, handheld, and implanted ECG monitors with accurate automated AF detection, the PiP approach with its inherent advantages has the potential to be more widely employed in clinical practice.

Disclosures

Debra Echt reports receiving consulting income and stock options from InCarda Therapeutics. Jeremy Ruskin reports receiving honoraria from InCarda Therapeutics, Acesion Pharma, Correvio, Huya Bioscience, and Pfizer.

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