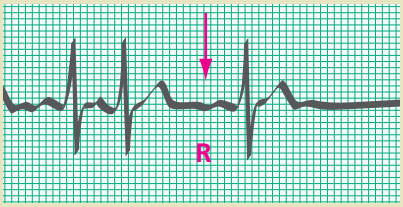
abstract



Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia worldwide, with an estimated prevalence of 0.4% in the general population. Despite recent advances in our understanding of the mechanism and consequences of AF, effective therapy for patients with AF remains difficult in many patients. Antiarrhythmic drug therapy includes control of ventricular rate as well as restoration and maintenance of sinus rhythm. The risks and benefits of each treatment modality must be assessed according to each individual patient's circumstances. Anticoagulation for stroke prevention is a critical component of AF management that is currently underprescribed. Anticoagulation with vitamin K antagonists, such as warfarin, remains the treatment of choice for preventing stroke and cardio embolism. The oral direct thrombin inhibitor ximelagatran has the potential to favourably influence the management of patients with AF by maximizing the potential of anticoagulation for stroke prevention.

Key words: *atrial fibrillation, anticoagulation, rate control, warfarin, ximelagatran, antiarrhythmic*

Atrial Fibrillation: Rate vs. Rhythm Control and Anticoagulation

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Introduction

In recent years, atrial fibrillation (AF) has been the subject of intense investigations in terms of obtaining a better understanding of its mechanism and improving its management. Since the early description of AF by Thomas Lewis in 1912,[1] it has been the overall perception that heart rate at rest in patients with AF should be controlled at a level close to that of patients with normal sinus rhythm.[2,3] Recent multicentre trials have suggested that rate control is a valid option for many patients with chronic AF.[4,5]

Cardiac output is a function of heart rate and stroke volume, but the relative contribution of each to cardiac output during rhythm changes and at different levels of activity is unclear. AF produces three important changes, all of which have an impact on the cardiac output: (i) loss of atrial contraction, (ii) irregular rhythm, and (iii) increased heart rate.[6]

Atrial contribution to ventricular filling has been found to vary from 0–41% and is mainly dependent upon left ventricular function.[7,8] Having an irregular rhythm instead of the regular rhythm at the same heart rate may lead to a reduction in stroke volume of approximately 10%.[9] Increased heart rate normally leads to an increase in cardiac output. It has been shown that an increase in heart rate during AF of 20–50% was often able to restore normal cardiac output at rest.[3] Rowles has shown that average heart rate for maximum cardiac output was 122 ± 29 beats/minute, whereas increasing the heart rate to above 140 beats/minute always led to a decrease in cardiac output. At the same time, observational studies have provided data suggesting that, over a prolonged period, a heart rate above 120 beats per minute may lead to left ventricular dysfunction.[10,11]

During the last 10 years, insight into the mechanism underlying AF has increased significantly, and many new treatment modalities such as catheter ablation, MAZE surgery, internal defibrillation, and pacemakers with preventative pacing algorithms have been developed. Despite this, the efforts to restore and maintain long-term sinus rhythm (rhythm control) is often time consuming and disappointing, and carries the risk of proarrhythmias and other adverse effects. On the other hand, accepting the arrhythmia and preventing the rapid ventricular rate during AF (rate control) can be performed in most patients with relative ease and effectiveness.[12]

Rate vs. Rhythm Control

Rhythm Control

Sinus rhythm (SR) is undoubtedly better than AF (Table 1).[12] During sinus rhythm, the heart is able to adapt its rate physiologically when an increased output is needed (e.g., during exercise, fever, and anaemia), and the atrium contributes to ventricular filling during each heartbeat. In contrast, during atrial fibrillation normal sinus node function and atrial

contribution to ventricular filling are lost, heart rate is increased and is irregular, and there is a risk of formation of (left) atrial thrombi. Because of this, AF can cause symptoms of palpitations, diminished exercise tolerance, dyspnea, angina pectoris, heart failure, and thromboembolic complications. Thus, a strategy to restore and maintain sinus rhythm appears appropriate.[12]

However, the recent Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial has led to a fundamental change in the therapeutic approach to patients with AF.[5] No longer is the goal of restoration of sinus rhythm sought for its own sake. In the AFFIRM population there was no improvement in mortality, stroke, quality of life, or the exercise tolerance in the cohort of patients who were randomly assigned to rhythm control as compared to the rate control. However so, rhythm control remains a viable treatment option. It seems reasonable to achieve symptom control in any individual patient by using the most efficacious strategy for the patient. Additionally, successful treatment of recurrent AF may represent a reduction of the arrhythmia burden, with symptomatic improvement rather than the complete elimination of AF.[5]

Table 1: Advantages and Disadvantages of Rhythm Control (vs. Rate Control)

Advantages
Physiological rhythm
Normal dromotropic response
Normal AV synchrony
Maintains atrial contribution to ventricular filling
No need for long term anticoagulation
Better hemodynamic, exercise tolerance
Better prevention of complications
Thromboembolic events
Structural and electrical remodelling
Better symptom relief
Disadvantages
Adverse effects of medications
Proarrhythmias
Sinus node, AV node dysfunction, pacemaker
Worsening of heart failure
Other (e.g., gastrointestinal thyroid function)
More hospital admission and higher cost
Risk of interventions
Electrical and chemical cardioversion
Ablation, maze surgery
Low success and high recurrence rates

Source: Wijffels MCEF et al., 2004.[12]

The main pharmacological agents used for rhythm control are class III agents—amiodarone, sotalol, and dofetilide.[13,14] The Canadian Trial of Atrial Fibrillation indicated a trend towards the superior efficacy of amiodarone when used at low doses.[15] The introduction of dofetilide has widened the therapeutic options in patients with severe heart disease. The release and development of newer class III antiarrhythmic agents may offer hope for the benefit of amiodarone without the serious adverse effects and long-term therapy.[16]

Other agents that have been used to treat AF are class IC agents—flecainide and propafenone[17]—and class IA agents. Quinidine and procainamide are of historical importance and are presently generally avoided due to their proarrhythmic and noncardiac adverse effect profile. Disopyramide has been used in the chronic therapy of AF and has been reported to be significantly effective in maintaining SR after cardioversion when compared to the placebo and also in patients with HCM; however, it has potential adverse events including Torsade de pointes, CHF from its negative inotropic effect, hypotension, and, additionally, glaucoma, urinary retention, prostatism in older males, and dry mouth because of its anticholinergic effects.[18]

Pure β-blockers and calcium channel blockers may have benefit in maintaining sinus rhythm in those patients who have been cardioverted from AF of recent onset. These agents lower the recurrence rate if initiated while the patient is in AF before cardioversion.[19] These effects may be the result of lowering intracellular calcium and thereby may reduce the electrical remodeling of the atria. Digoxin does not alter the probability of cardioversion or the maintenance of SR. In patients with reduced Left Ventricular Ejection Fraction (LVEF) secondary to prior myocardial infarction therapy with ACE inhibitor, trandolapril can reduce the incidence of AF relative to placebo.[20] This treatment effect observed with angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) may be because of the role the renin-angiotensin-aldosterone system plays as a mediator of atrial remodeling in AF and not directly by the blood pressure lowering effect.[21]

However, the optimal antiarrhythmic drug therapy needs to be individualized based on symptomatology, inpatient or outpatient treatment, associated cardiac and systemic comorbidities, age, and adverse effect profiles. Specific harmful effects include drug-induced proarrhythmias, bradyarrhythmias, negative inotropic affected organ toxicity, and a negative impact on mortality.[16,17,22]

Rate Control

Although sinus rhythm, in theory, is better than AF, it should be stressed that the strategy of rhythm control is not equivalent to sinus rhythm. To restore and maintain sinus rhythm, electrical cardioversion, antiarrhythmic drugs, and other invasive treatment such as ablation or surgery are often needed. This carries the risk of adverse drug effects including proarrhythmias, sinus node dysfunction, heart failure, and other iatrogenic risks.[12] Also, despite all these efforts, the rate of recurrence remains high in many patients due to failure of rhythm control. In contrast, rate control that results in good symptom relief in patients is much easier and carries less risk for adverse events.

Young patients with a good exercise tolerance (NYHA class 1-II), AF less than three months, and without hypertension have a fair chance of maintaining sinus rhythm after single cardioversion.[23] In contrast, in patients older than 70 years of age with AF greater than 36 months and poor exercise tolerance, the long-term success rate for maintenance of sinus rhythm is very low. Thus, rate control is a better option in these patients.[24]

Several randomized controlled trials have prospectively addressed the issue of whether rhythm control is indeed better than the rate control in patients with AF. The largest among them, the AFFIRM trial,[5] screened 7,401 patients of at least 65 years with recurrent AF and risk factors for stroke and death. The risk factors included a history of hypertension (treated or untreated), diabetes, and congestive heart failure; a prior history of stroke; transient ischemic attack; systemic embolus; a left atrial short axis dimension of ≥50mm; a left ventricular shortening factor of <25% by echo; or LVEF of <40% by any technique. A total of 4,060 patients were randomly assigned to rate control or rhythm control strategy. In more than two-thirds of patients, the qualifying episode of AF had lasted for more than two days. Similar to the design of other trials, digoxin, calcium channel antagonists, and/or β-adrenergic blockers were used for rate control in 2,027 patients assigned to that treatment arm. Electrical cardioversion and an array of class IA, IC, and III drugs (including amiodarone) were used for the patients assigned to the rhythm control arm (2,033 patients). Oral anticoagulation was adjusted to maintain the INR of 2.0 to 3.0, which could be stopped if sinus rhythm had been present for more than four weeks. The mean follow-up time was 3.5 years.

At five years, sinus rhythm was the rhythm documented at the follow-up visit in 35% of the rate-controlled patients compared with 65% of the rhythm-controlled patients. Total mortality (primary endpoint) was 17.5% for patients assigned to the rhythm control and 15.3% for rate control (P=0.08). There was no difference in the composite secondary endpoints (death, disabling stroke, anoxic encephalopathy, major bleeding complications, or cardiac arrest). The rhythm-controlled patients were hospitalized more frequently (P<0.001) and had more adverse drug effects (P<0.004). Bleeding complications were associated with higher international normalized ration (INR) values (4.3 ± 4.9). Most thromboembolic events occurred after discontinuation of anticoagulants or at subtherapeutic INR values. Interestingly, 69% of the rate-controlled patients and 36% of the rhythm-controlled patients with ischemic strokes were in AF at the time of presentation with this complication. There was no difference in the quality-of-life measures in the two arms of this minimally symptomatic population. A recent post hoc analysis of four major studies showed that the stroke incidence was significantly higher with rhythm-controlled therapies compared with rate control therapy.[25] However, this adverse outcome may be due to the fact that, contrary to the recommendations from current guidelines, oral warfarin anticoagulation was discontinued in many patients who appeared to be maintaining sinus rhythm despite the presence of stroke risk factors.

The major trials thus showed that rhythm control is not superior to rate control. In fact, these trials suggest that rhythm control strategies may show a trend towards increased morbidity and mortality that may be caused by the adverse effects of antiarrhythmic drugs and the need for cardioversions.[12] In addition, these trials suggest the importance of adequate anticoagulation and indicate that simple restoration of sinus rhythm does not warrant discontinuation of oral anticoagulant therapy.[12]

Therefore, the decision to choose rhythm or rate control strategy should be individualized and should depend on the expected benefit of restoring sinus rhythm and the likelihood of adverse drug effects. In all patients with AF, treatment should focus on underlying heart disease, anticoagulation, and control of ventricular rate during AF.

Anticoagulation for Atrial Fibrillation

AF is common among older people who are at higher risk for stroke, and it can be estimated that approximately 14% of all strokes in the United States are attributable to AF.[26] AF remains a powerful risk factor for thromboembolism, raising the risk of ischemic stroke five-fold. Thromboembolism from the left atrium (LA) appears to be the predominant mechanism for AF-related ischemic strokes.[27] Research conducted over the last few years has demonstrated that oral anticoagulation is highly effective in reducing the risk of stroke in AF, presumably by reducing left atrial appendage thrombi.[28] Primary prevention trials comparing anticoagulation to no anticoagulation have shown the superiority of the former in preventing stroke associated with AF.[29] Anticoagulants were shown to dramatically reduce the risk of stroke with pooled relative risk reduction of 68%. The absolute reduction in risk was 3.1% per year with a 4.5% annual stroke rate for control patients compared with 1.4% for patients taking anticoagulants. Anticoagulants also significantly reduced the all-cause mortality by 33%. The initial trials have demonstrated that anticoagulation achieving INR levels primarily in the 2.0–3.0 ranges are effective and acceptably safe.[29]

A number of randomized trials directly compared acetylsalicylic acid with adjusted dose anticoagulation in patients with AF to prevent strokes. A meta-analysis from these trials using pooled individual patient level data found that anticoagulants were more effective than acetylsalicylic acid in decreasing the rate of all strokes with a hazard ratio (HR) of 0.55, with an HR 0.48 for ischemic strokes, and an HR 0.71 for cardiovascular events.[30] However, anticoagulation was associated with a higher risk of major haemorrhage compared with acetylsalicylic acid. Overall, the meta-analysis estimated that treatment with oral anticoagulation versus acetylsalicylic acid would prevent 23 ischemic strokes per 1,000 patients per year while causing nine major bleeding events. Both the meta-analysis and a

more recent and powerful assessment of stroke outcome in AF make clear that disabling, presumably embolic, strokes are prevented far better by adequate anticoagulation than by low intensity anticoagulation or acetylsalicylic acid.[31] Thus, not only does anticoagulation above INR 2.0 prevent more strokes than acetylsalicylic acid, it also appears superior for preventing disabling or fatal strokes. The optimal anticoagulant study for now appears to be between INR 2.0 and 3.0.[28] In summary, randomized trials have demonstrated that oral anticoagulation is significantly and substantially more effective than both placebo and acetylsalicylic acid in the prevention of stroke for AF.

The NASPEAF trial (National Study of Prevention of Embolism in Atrial Fibrillation) has assessed the efficacy of cyclogenase inhibitor trifusal (600 mg per day, roughly equivalent to acetylsalicylic acid 300 mg per day) in combination with near-standard intensity anticoagulation (INR 1.5–2.4) versus anticoagulation targeted at the standard INR of 2.0–3.0. Preliminary reports of the study indicated that the combination of antiplatelet agents and modestly reduced–intensity anticoagulation (mean INR 2.0) was actually superior to the standard anticoagulation at INR 2.0 to 3.0.[32]

The American College of Cardiology /American Heart Association/ European Society of Cardiology (ACC/AHA/ESC) guidelines[33] have laid out recommendations for the use of acetylsalicylic acid and anticoagulants (Table 2 and Figure 1).

There has been some reluctance to offer anticoagulant therapy to older patients with AF because of the perceived inability to adequately regulate INR status because of aging. Hylek *et al.*[34] studied 4,517 outpatients who were taking warfarin for AF, with most managed by their primary care physicians. The authors reviewed the quality of INR control according to age by measuring time in therapeutic range (INR 2.0–3.0), at an INR above 5.0 and at INR below 1.5. They found no difference among age groups younger than 65, 65 to 74, 74 to 84, and older than 84 years in the percentage of time in the therapeutic range or well above and below the therapeutic range. Therefore, it does not appear to be more inherently difficult to maintain INRs in the therapeutic range as persons get older.

Recognizing that the increased risk of bleeding is a major disadvantage of anticoagulant therapy and that older age may confer a slightly higher risk of developing anticoagulant related bleeding complications, it must be remembered that of all age groups, patients older than 65 years are also at the higher risk of stroke from AF.[35] Therefore, as described by Hart,[36] older patients with AF not only have the most to gain from the treatment with anticoagulant agents but also potentially have the most to lose. Considering that many studies have shown that among all age groups, older persons with AF are the least likely to receive anticoagulant therapy, it seems that many clinicians are overly concerned about the possible negative effects of anticoagulant therapy and tend to underemphasize its potential benefits.[37,38,39]

The ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) study was a randomized comparison of conventional periprocedural anticoagulation with TEE-guided cardioversion of AF.[40] This study observed similar low rates of emboli using either strategy, although rates of hemorrhage were lower in the TEE–guided arm because the period of anticoagulation was shorter.

Current recommendations are to give three weeks of anticoagulation at INR range of 2.0–3.0 precardioversion and four additional weeks of anticoagulation after sinus rhythm has been restored. An alternate strategy would be immediate cardioversion with periprocedural anticoagulation if no left atrial thrombi are noted on TEE, followed by four weeks of anticoagulation. Cardioversion without anticoagulation may also be accepted if the duration of AF is less than two days, although this last exclusion is not based on firm clinical evidence.[29]

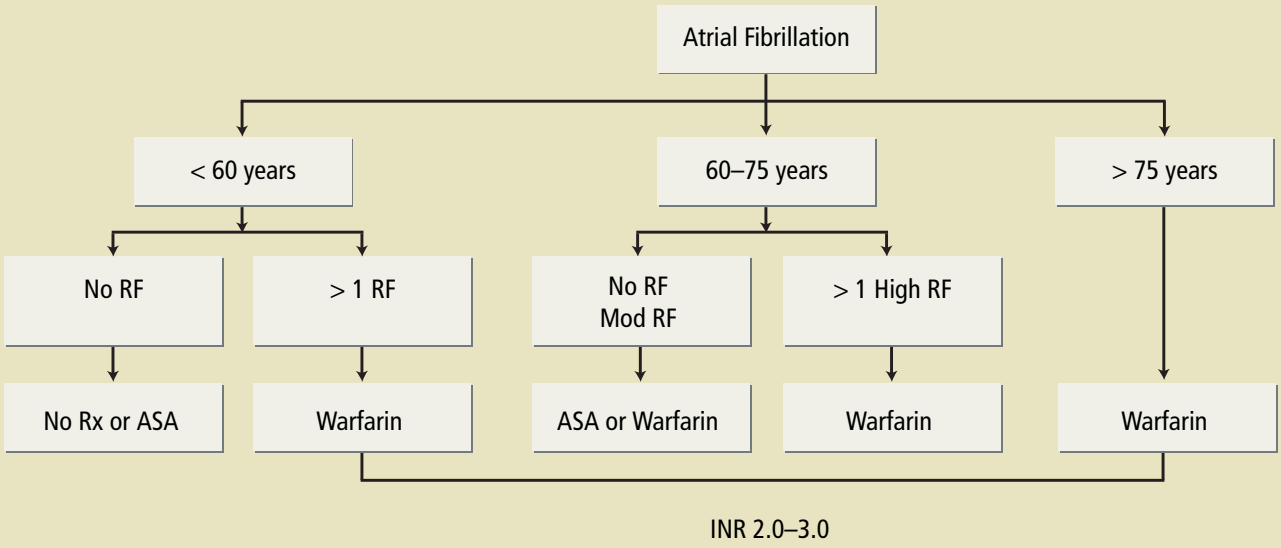
Several newer oral anticoagulant agents have been developed, including the fixed–dose direct thrombin inhibitor ximelagatran (Table 3). Ximelagatran, an oral direct thrombin inhibitor, is a prodrug of melagatran. After oral administration, ximelagatran is absorbed from the gastrointestinal tract with a bioavailability of 20%, and plasma levels peak approximately 30 minutes after drug ingestion.[41] Although ximelagatran has no intrinsic anticoagulant activity, it is rapidly transformed to melagatran, a small molecule

Table 2: American College of Cardiology /American Heart Association / European Society of Cardiology Treatment Guidelines

Anticoagulation at INR 2.0 to 3.0 for patients with AF and
• age 75 years or older (especially women)
• younger patients with risk factors for thromboembolism
• a prior thromboembolism, hypertension, diabetes, LVEF ≤35%, heart failure, thyrotoxicosis, persistent atrial thrombus on TEE, mitral stenosis and prosthetic heart valves (higher INR targets may be needed for the last risk factor).
• age ≥60 years with diabetes mellitus or CAD
Aspirin 325 mg daily for patients with AF and
• age ≥60 years and no risk factors for thromboembolism.
• age ≤60 years and no heart disease (lone AF)
• age ≤60 years with heart disease but no risk factors for thromboembolism.

Adapted from ACC/AHA/ESC Task Force on Practice Guidelines, 2001.[33]

Figure 1: Stratification for Antithrombotic Therapy by Risk Factors (RF) in Patients with AF



High RF

- Prior TIA or stroke
- Hypertension
- Heart failure
- Mitral stenosis
- Prosthetic heart valve

Moderate RF

- Coronary artery disease
- Diabetes mellitus

RF: Risk Factor, ASA: Acetylsalicylic acid, Rx: Treatment, INR: International normalized ratio, TIA: Transient ischemic attack

(Adapted from: Voller H, 2005[48] and ACC/AHA/ESC guidelines[33])

that targets the active site of thrombin and blocks the enzyme's catalytic activity. Plasma levels of melagatran peak at two hours after drug ingestion. The drug has a half-life of four to five hours in patients and should therefore be administered twice daily.[25] Melagatran is excreted primarily via the kidneys. Therefore, its half-life is prolonged in patients with a creatinine clearance <30 ml/min. However, dosing requirements do not vary with age, gender, ethnicity, obesity, or food or alcohol intake and, therefore, ximelagatran is given in fixed doses to most patients. Oral ximelagatran also exhibits a low potential for interaction with other medications.[42,43] Ximelagatran produces such predictable anticoagulant responses that coagulation monitoring is unnecessary, making it an attractive candidate to evaluate as an alternative to warfarin in patients with AF.[44] Two SPORTIF trials (Stroke Prevention using an Oral Thrombin Inhibitor in atrial Fibrillation) compared ximelagatran (36mg twice daily), administered without coagulation monitoring, to dose-adjusted warfarin (target INR 2.5, range 2.0–3.0) in patients with nonvalvular AF and at least one additional risk factor for stroke. The SPORTIF III trial[45] used an open-label design with blinded endpoint adjudication, whereas the SPORTIF V trial[46] was a double-blind trial using a sham INR scheme to maintain blinding. Preliminary reports indicate that fixed-dose ximelagatran may be as safe and effective as dose-adjusted warfarin in preventing stroke and systemic embolism. Results from this trial will help define the role of ximelagatran in preventing stroke in AF. Outcome measures were the same in both the trials: the primary efficacy outcome was a combination of all strokes (ischemic and hemorrhagic) and systemic embolic events, whereas the primary safety endpoint was bleeding, which was classified as major or minor. Both studies were designed as noninferiority trials to demonstrate that ximelagatran was at least as effective and tolerated as warfarin.

In both the SPORTIF III trial[45] (which enrolled 3,407 patients) and SPORTIF V trial[46] (which enrolled 3,922 patients) the rate of major bleeding was similar in the ximelagatran and warfarin groups but the rate of major plus minor bleeding was lower with ximelagatran than with warfarin. In prespecified analyses of the pooled data from SPORTIF III and SPORTIF V trials, the absolute difference in the rate of stroke and systemic embolic events was 0.03% lower in those given ximelagatran relative to those receiving warfarin, but this finding was nonsignificant. Rates of major bleeding with ximelagatran and warfarin were 1.9 and 2.5% per annum, respectively. Using a composite endpoint of all strokes, systemic

Table 3: Comparison of Warfarin, Ximelagatran, and Low Molecular Weight Heparin

	Warfarin	Ximelagatran	Idraparinux (LMWH)**
Delivery	Oral	Oral	Subcutaneous
Mechanism of action	Attenuates thrombin generation by reducing levels of vitamin K–dependent clotting factors	Melagatran binds thrombin and blocks its activity	Catalyses factor Xa inhibition by antithrombin
Onset of action	Delayed for three to five days	Rapid: drug levels in two hours	Rapid: drug levels in two hours
Drug interactions	Multiple	None	None
Food interactions	Influenced by vitamin K content in diet	None	None
Need for coagulation monitoring	Yes	No	No
Dosing	Variable and dictated by INR* results	Fixed	Fixed
Antidote	Vitamin K	None	None
Drug induced elevation in serum transaminases	Rare	Occurs in about eight percent of patients treated long term.	None

Adapted from O'Donnell et al., 2005.[44]
*INR: International normalized ratio, **LMWH: Low molecular weight heparin

emboli, major bleeding, and death, ximelagatran produced a 16% relative risk reduction compared with warfarin. On the basis of SPORTIF III and SPORTIF V trials, ximelagatran, with no need for coagulation monitoring, appears to be as effective and safe as dose-adjusted warfarin.

Ximelagatran is an orally active direct thrombin inhibitor that has undergone numerous phase III trials as a possible alternative to warfarin and other anticoagulants. While study results have been generally positive, concerns over trial design, possible increase risk of coronary events with short term use, and possible drug-induced liver failure associated with long-term use have kept the agent from being approved by FDA for marketing in the United States.[47]

Conclusion

Atrial fibrillation remains a major risk factor for stroke. Thromboembolism is a major complication in AF, prevention of which constitutes a major challenge in the modern treatment of this common arrhythmia. Recent studies show that treatment strategies that combine control of ventricular rate with antithrombotic therapy are as effective as those strategies aimed at restoring sinus rhythm. Furthermore, even when rhythm control strategies are employed, recurrent AF occurs with sufficient frequency to warrant ongoing antithrombotic therapy. Currently, however, the options for antithrombotic therapy for AF are limited and involve chronic anticoagulation with dose-adjusted vitamin K antagonists, unless patients have a contraindication to these agents or are at low risk for stroke. AF patients with low risk for stroke may benefit from acetylsalicylic acid. Although vitamin K antagonists are effective, their use is problematic, highlighting the need for new antithrombotic strategies. Of the new anticoagulants under investigation in AF, ximelagatran is at the most advanced stage of development and on the basis of the data available to date appears to be a suitable alternative to vitamin K antagonists. In fact, the oral bioavailability, a predictable anticoagulant response to fixed dose, and the lack of anticoagulation monitoring make ximelagatran easier to administer. However, the issues that still need to be addressed include elevation of liver enzymes (its most common side effect), the lack of an antidote, and cost. Ximelagatran is likely to be the first alternative to warfarin. The availability of this new agent has the potential to increase the use of anticoagulation therapy in patients with AF, thereby reducing morbidity and mortality from stroke.

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