Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, it affects about 2% of the population and its prevalence increases with age up to 15% at 80 years [1-3].

Atrial fibrillation is not a benign disease, it is strongly associated with adverse clinical outcomes, including stroke, heart failure, reduced exercise capacity and quality of life, and doubles the risk of death [4-5].

Drug therapy for atrial fibrillation aims to reduce those adverse events and to slow the progression of the disease, from short and rare episodes to longer and more frequent attacks ending by the permanent form of atrial fibrillation.

**ANTICOAGULATION IN ATRIAL FIBRILLATION**

Stroke in atrial fibrillation is often severe and results in long-term disability [4, 6] and the risk is the same for paroxysmal, persistent or permanent AF [7].

The vitamin K antagonist (VKA), warfarin is significantly superior to aspirin [8] or the combination of aspirin and clopidogrel [9] without an increased risk of bleeding (target INR 2-3).

The oral direct thrombin inhibitor, dabigatran etexilate at 110 mg BID was non inferior to VKA for the prevention of stroke and systemic embolism with lower rates of major bleeding, and at 150 mg BID was more effective than VKA with the same risk of bleeding according to the RE-LY study [10].

In the ROCKET AF trial, the oral direct factor Xa inhibitor rivaroxaban, at 20 mg OD was non inferior to warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation. There was no significant difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group [11].

The indication for anticoagulation should be based on the presence of risk factors for stroke according to the CHA₂ DS₀-VASc score: cardiac failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74 and sex category (female) [12].

Oral anticoagulation is recommended for a score ≥ 2 while aspirin or oral anticoagulation is recommended for a score of 1 and aspirin or no antithrombotic therapy at all for a score of 0.

**RATE CONTROL VERSUS RHYTHM CONTROL**

Concerning the treatment of the arrhythmia there are two strategies:

* The rate control strategy: keep atrial fibrillation but control the ventricular rate.
* The rhythm control strategy: try to keep the patient in sinus rhythm.

All published studies have shown that rate control is not inferior to rhythm control for the prevention of mortality and morbidity [13-18].

The disappointing outcome of the rhythm control strategy may be related to the low maintenance rate of sinus rhythm in the rhythm control groups, 63% after 5 years in the AFFIRM trial [13], and 39% after 2.3 years in the RACE trial.

The negative outcome with rhythm control may also be secondary to the selection of patients that are not very symptomatic when in AF according to the EHRA score, and sometimes withdrawing the anticoagulation therapy from patients in the rhythm control arms based on the assumption that sinus rhythm was present, resulting in a potentially avoidable excess risk of ischemic stroke.

In addition, a subgroup analysis of the AFFIRM database has suggested that deleterious effects of antiarrhythmic drugs (AADs, a mortality increase of 49%) may have offset the benefits of sinus rhythm (which was associated with a 53% reduction in mortality).

Current guidelines base the decision to add rhythm control therapy to the management of AF on individual factors interpreted by the physician and the patient (symptoms according to the EHRA score, history of the AF, age, probability of a successful rhythm control strategy and other associated medical conditions).

**RATE CONTROL STRATEGY**

Drugs commonly used for rate control are ß-blockers, non-dihydropyridine calcium channel antagonists and digitalis.

* ß-blockers are the first line treatment and are especially useful in the presence of high adrenergic tone or symptomatic myocardial ischemia occurring in association with AF.
  * Non-dihydropyridine calcium channel antagonists
(verapamil and diltiazem) are effective for rate control of AF but should be avoided in systolic heart failure because of their negative inotropic effect.

- Digoxin is effective for the rate control at rest but not during exercise. It is frequently combined with other rate control medications but may cause serious adverse side effects and should be used cautiously.

Concerning the intensity of rate control therapy, the RACE II trial [19] didn’t show any benefit of stringent rate control over lenient rate control therapy. Lenient rate control used a resting heart rate < 110 bpm as the therapeutic target. While stringent rate control aimed at a resting heart rate of < 80 bpm and < 110 bpm during moderate exercise.

RHYTHM CONTROL STRATEGY

The class IA antiarrhythmic drugs (e.g. quinidine, procainamide, disopyramide) are no longer recommended for the treatment of atrial fibrillation because a previous synthesis of evidence concluded that they are potentially harmful for the patients probably because of the proarrhythmic effect [20]. The antiarrhythmic drugs that can be used for pharmacological cardioversion of a recent onset atrial fibrillation are mainly the class IC agents flecainide and propafenone, the class III amiodarone and ibutilide and the new AAD vernakalant.

Flecainide given IV at 2 mg/kg in 10 minutes can restore sinus rhythm in new onset atrial fibrillation in up to 95% of the patients within few hours [21]. A single oral loading dose (200-300 mg) has a conversion rate of 50-60% at 3 hrs and 75-85% at 6-8 hrs [22-24].

With propafenone, the expected conversion rate was between 41-91% after IV use (2 mg/kg over 10-20 min) in 30 min to 2 h and its also effective if administered orally at 450-600 mg (conversion between 2 and 6 hrs).

Flecainide and propafenone should be avoided in patients with underlying heart disease involving abnormal left ventricular function and ischemia [25-27] because of the proarrrhythmic and negative inotropic effect. In addition, because of its β-blocking properties, propafenone should be avoided in severe obstructive lung disease. The I-C AADs may inadvertently increase the ventricular rate due to conversion of the AF to atrial flutter with 1:1 conduction to the ventricles. This is why they should always be used with AV node blockers.

Amiodarone is recommended in the presence of structural heart disease but the cardioversion occurs several hours later than with flecainide or propafenone (5 mg/kg IV over 1 hr than 50 mg/hr).

Ibutilide (2 doses of 1 mg IV over 10 min each) has demonstrated conversion rates of 50% in 90 min but there is a risk of QT prolongation and of polymorphic ventricular tachycardia (non-sustained ventricular tachycardia in 10% of the patients) [28].

Vernakalant is a new AAD recently approved for cardioversion of new onset AF, the conversion rate to sinus rhythm is 51% at 90 min after an initial bolus of 3 mg/kg over 10 minutes then 2 mg/kg over 10 min (15 min of observation between the two doses).

Vernakalant is contraindicated in the presence of hypotension, severe aortic stenosis, severe heart failure (class NYHA III and IV) or an acute coronary syndrome within the previous 30 days [29-31].

ANTIARRHYTHMIC DRUGS

FOR MAINTENANCE TREATMENT

Outside the acute phase, the physician should discuss with his patient about the optimal strategy for the long term management of the atrial fibrillation. If the rhythm control strategy is chosen, the patient can use the pill-in-the-pocket approach for symptomatic but infrequent recurrences of AF (between once per month and once per year) or take the AADs on a daily basis if the arrhythmia is more frequent.

When choosing an AAD for the long-term management we should think about:

- The efficacy of the drug
- The possible side effects
- The drug induced pro-arrhythmia
- The effect on mortality, morbidity and hospitalization.

FLECAINIDE

Flecainide at 100-200 mg BID or flecainide XL 200 mg OD doubles the likelihood of maintaining sinus rhythm. It can be safely used in patients without significant structural heart disease or coronary artery disease. Precautions should be observed when using flecainide in the presence of wide QRS, particularly LBBB.

Upon initiation of therapy, regular ECG monitoring is recommended. If the QRS duration increases by more than 25% the drug should be stopped or the dose reduced because of the potential risk of pro-arrhythmia.

Flecainide is also contraindicated if the creatinine clearance is less than 50 mg/ml.

PROPafenONE

The recommended maintenance dose is 150-300 mg TID or propafenone SR 225-425 mg BID. By analogy to flecainide, propafenone should not be used in patients with coronary artery disease or reduced LVEF. QRS duration should also be monitored like with flecainide.

The class IC should always be used with AV node blockers because of the potential transformation of AF to atrial flutter with 1:1 conduction.

SOTALOL

In the Safe-T study [32] sotalol and amiodarone were equally efficacious in converting AF to sinus rhythm but amiodarone was superior for maintaining sinus rhythm.
Both drugs have similar efficacy in patients with ischemic heart disease.

Sotalol is not recommended in the presence of left ventricular hypertrophy or significant left ventricular dysfunction because of the risk of pro-arrhythmia by increasing the QT interval.

It is also contraindicated in the presence of renal failure with creatinine clearance < 50 mg/ml or pre-existing QT prolongation. The recommended dose is 80-160 mg BID (stop if QT > 500 ms).

AMIODARONE

A big meta-analysis showed that amiodarone is more effective than sotalol, propafenone, flecainide [33] and dronedarone in maintaining sinus rhythm [34-40]. It is also the only AAD that can be used in the presence of severe heart failure (NYHA class III/IV or unstable class II) because of the increased major adverse cardiac events of the other AAD drugs including dronedarone [41].

The recommended dose of amiodarone is 600 mg for 4 weeks, 400 mg for 4 weeks then 200 mg OD (a more rapid loading up to 1600 mg daily for 7 days can be used if necessary). With a frequent monitoring of the QT interval (decrease the dose if QT > 500 ms).

The problem of amiodarone is the extra cardiac toxicity:

There is a 1% risk of pulmonary toxicity per year and it is probably dose related. Amiodarone can also cause hypothyroidism (about 6% during the first year of treatment) and hyperthyroidism (0.9%).

Regarding central nervous system side effects, the patient can develop proximal muscle weakness, peripheral neuropathy, headache, ataxia, tremors and impaired memory. We notice also an increase of liver function enzymes in 10 to 20% of patients, photosensitivity that increases with sun exposure and corneal micro deposits.

Amiodarone also has drug interaction with many cardiac medications; it prolongs the prothrombin time and may cause bleeding in patients on warfarin. Amiodarone increases the plasma digoxin concentration, predisposing to digitalis toxic effects.

Amiodarone also has a β-blocking effect that can cause bradyarrhythmias.

DRONEDARONE

Dronedarone is a benzofuran derivative with anelectropharmacologic profile resembling that of amiodarone but with different relative effects on individual ion channels. The structural changes made to amiodarone to produce dronedarone decreases lipophilicity, thus shortening the half-life (to approximately 24 hrs) and reducing accumulation in tissue. Molecular changes were made also to reduce the risk of amiodarone-associated thyroid-related and pulmonary disease. Dronedarone is hepatically metabolized and excreted in the feces.

Dronedarone was shown in two large pivotal trials to be superior to placebo in maintaining sinus rhythm in patients with recurrent AF [42].

In the DIONYSOS trial [43], dronedarone was less efficacious in maintaining sinus rhythm in patients with AF compared to amiodarone, but also less toxic (fewer thyroid, neurological, skin and ocular events).

The ANDROMEDA trial [41] evaluated the use of dronedarone in patients with symptomatic (NYHA Class II-IV) heart failure, who in addition had severe left ventricular dysfunction and at least one NYHA Class III-IV episode requiring hospitalization in the past month. The study was stopped prematurely due to increased mortality with dronedarone.

The ATHENA trial [44] evaluated the efficacy of dronedarone 400 mg BID (compared to placebo) for the prevention of cardiovascular hospitalization or death from any cause in patients with AF and cardiovascular risk factors. The study was able to demonstrate a lower hospitalization, cardiovascular mortality and stroke rate in the dronedarone arm.

Finally, the PALLAS trial published lately evaluated the effect of dronedarone on top of standard therapy for patients with permanent AF who were at high risk for vascular events. Unfortunately, the study was stopped for safety reasons because of the increased rates of heart failure, stroke and death from cardiovascular causes in the dronedarone group [45].

The conclusion of all those studies on dronedarone would be to use dronedarone for patients with non permanent AF but avoid the patients with severe heart failure (NYHA Class III-IV or unstable Class II) or recent hospitalization for decompensation of heart failure.

UPSTREAM THERAPIES FOR ATRIAL FIBRILLATION

Upstream therapy refers to the use of non-antiarrhythmic drugs that modify the atrial substrate- or target-specific mechanisms of AF to prevent the occurrence (primary prevention) or recurrence (secondary prevention) of the arrhythmia. Such agents include: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), statins, n-3 (w-3) polyunsaturated fatty acids, and possibly corticosteroids.

Upstream therapy is discussed separately (pp. 105-108).

CONCLUSION

Therapeutic approaches to atrial fibrillation emphasize three main aspects:

- Anticoagulation according to the risk factors for thrombosis and bleeding.
- Cardioversion with maintenance of sinus rhythm by antiarrhythmic agents all having potentially serious side effects.
- Accepting chronic atrial fibrillation with the emphasis on rate control.

While waiting for the “perfect” medication for atrial fibrillation, the decision about the treatment should be
based on the risk and benefit evaluation of each situation with a close follow-up and continuous reassessment of our patients if their medical condition changes.

REFERENCES


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