



abstract ■ **Objective:** evaluate the advantages and inconveniences of rhythm, control compared to rate control in the management of atrial fibrillation (AF). **Materials and methods:** a review of clinical trials evaluating the results of the strategies to control rhythm or heart rate in the management of atrial fibrillation available in Medline updated 15 November 2011. **Results and conclusions:** rhythm control strategies have not shown to be superior to rate control strategies and can lead to adverse effects and higher rates of hospital admissions. There is an excessive use of rhythm control strategies in clinical practice. Rhythm control should be used in cases of poor rate control, young patients or with low risk of recurrence of AF and the presence of AF caused by a reversible process. Adverse effects of antiarrhythmic agents, careful selection of the adequate drug and candidates for ablation should be considered. Rhythm or rate management strategies can be complementary. The most important aims include appropriate management of the underlying disease, symptom management, prevention of thromboembolism and the development of AF. **Key words:** atrial fibrillation, heart rate, cardiac rhythm, antiarrhythmic agents

Atrial fibrillation, rhythm or rate control?



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Introduction

The strategy of *heart rate control versus rhythm control* in atrial fibrillation (AF) is one of the most controversial issues in the last few years. The recently published guidelines¹⁻³ do not clearly resolve this issue. Moreover, it is one of the chapters in medicine that currently pose important divergences between the existing evidence and what occurs in reality of clinical practice. Before addressing the issue in depth, it is important to outline some aspects:

- The issue is a target for controversy^{4,5} and the author of this paper is a specialist who, with given the currently available management options, defends the strategy of rate control compared to rhythm control.

- The main objective of the management of patients with AF is not the decision on rhythm control versus rate control. The most important objectives are appropriate treatment of the underlying disease, symptom management, prevention of thromboembolism and the important challenge of avoiding the progression of the AF⁶.

- The debate is not in the discussion of whether the best option is sinus rhythm or AF, because this is obvious, but rather whether the current therapeutic options available to maintain sinus rhythm are really effective and safe and represent a better alternative to a rate control strategy.

- With regard to clinical practice, working with homogenous protocols is important but it is not that simple in the case of AF, where multiple factors play an important role. It is not correct or possible to treat all patients with AF equally and in many occasions both strategies discussed here are complementary. For this reason, management should be individualized, for that the following factors should be considered:

- Age of the patient.
- Symptoms caused by the FA

- Underlying disease and repercussion of AF on the disease.
- Probability of maintaining AF.
- Classification of AF according to duration:
 - Paroxysmal AF (up to 7 days, normally < 48 hours)
 - Persistent AF (7 days or requires cardioversion)
 - Long standing persistent AF (1 year)
 - Permanent AF (acknowledged AF, no attempt of cardioversion)

Reasons offered to defend a rhythm control strategy compared to rate control

Rhythm control reduces embolic risk

The most important repercussion of AF in the population is the increased risk of embolism, for which the majority of patients with AF are under treatment with anticoagulation. The hypothesis is that a rhythm control strategy would be useful to reduce embolism risk has failed miserably and has supposed a painful lesson in both clinical trials and clinical practice.

In the AFFIRM trial⁷, withdrawal of treatment with oral anticoagulation was allowed after authorization by doctors in the rhythm control group. In these patients a higher rate of stroke was observed, although with no statistical significance. In 78% of the cases of stroke, patients were not taking warfarin (58%) or presented INR levels of less than 2 (20%). It is also worth mentioning that from all patients in the rhythm control group who suffered a stroke, only 36% presented AF at the moment when the event occurred. The stroke protective effect was not the management strategy of rhythm control, but rather warfarin treatment. These data should not surprise us because we know that paroxysmal AF maintains an embolic risk⁸⁻¹⁰, and therefore in the stratification of embolic risk of AF like the CHADS2 and the CHAD2DS2-VASc score calculators (tables 1 and 2) there are no data on whether the patient presents sinus rhythm or AF.

Why doesn't the rhythm control strategy reduce the thromboembolism risk? There are at least two reasons. In the first place, with the methods available, the recurrence of AF is frequent and in many occasions asymptomatic. Secondly, in some occasions, patients with AF present other risk factors of thromboembolism and AF in these patients is more representative of a risk marker rather than a risk factor.

Despite the available evidence, one of the most frequent errors in clinical practice still is failing to indicate oral anticoagulation in patients with paroxysmal AF dismissing the embolism risk¹⁰, and resulting in negative consequences for patients.

Therefore, we should recall that the indication for oral anticoagulation is based on the presence of risk factors of embolism but not on the persistence or not of AF. The choice of a rhythm control strategy does not avoid oral anticoagulation.

Rhythm control leads to better hemodynamic conditions that benefit especially those patients with heart failure

It is obvious that the hemodynamic condition of the heart in sinus rhythm is better than one in AF and we know that in patients with heart failure, the co-existence of AF implies a worse prognosis^{11,12}. For this reason, a hypothesis has been posed that in patients with heart failure, the rhythm control strategy could be superior to a heart rate control strategy. It has been criticized that this population was not well represented in comparative studies of these two strategies^{7,13-16}. However neither in the AFFIRM trial¹⁷ nor in the RACE trial¹⁸ were there differences in the progression to heart failure among both groups, rhythm control versus rate control.

Perhaps the ideal population to demonstrate this hypothesis is the patient with heart failure with systolic dysfunction. The AF-CHF study¹¹ responds to this question. It includes more than 1300 patients with symptoms of heart failure, systolic dysfunction with an ejection fraction $\leq 30\%$ and a history of AF, followed up for a period of 3 years. The cardiovascular mortality (primary endpoint) was similar in both groups and the secondary endpoints were also similar, including worsening of heart failure condition. Nor was there any benefit in rhythm control observed in the pre-specified subgroups. A meta-analysis¹⁹ found similar mortality, stroke or peripheral embolism rates in both strategies. In the rate control strategy there were less hospital admissions. There is no information with respect to heart failure due to diastolic dysfunction.

The choice of a rhythm control strategy does not avoid the need for oral anticoagulation, which should be based according to the risk of embolism

What could the reason be why rhythm control does not prove to be superior to rate control in this population? A few reasons could be given, such as the deleterious effects of the antiarrhythmic drugs, the difficulty in maintaining sinus rhythm in the mid to long term in these patients, and lastly the probability that the prognosis of these patients is not determined by the AF but rather the underlying disease and its evolutionary state.

It has been proposed that AF ablation could offer more favourable results in order to avoid the risk of antiarrhythmic drugs and achieve greater success in the maintenance of sinus rhythm. Although some studies show a possible benefit in ablation in patients with heart failure²⁰⁻²², its role is not well established and long-term studies on this issue are necessary. In any case, it should be noted that success of ablation in this population is lower than in other populations and thus an important factor to bear in mind is the selection of more appropriate patients. Moreover, it is known that AF ablation is a complex technique and patients undergo greater risk than with other types of ablation and it is not easy to generalize its use in a wider population.

Therefore, in the majority of patients with heart failure and AF, it is preferable to adopt an initial rate control strategy with the aim of maintaining baseline rate of 80 beats per minute (bpm) while in the 6-minute test a rate of less than 110 bpm. Rhythm control strategy can be proposed in cases of important deterioration of patients condition on developing AF, suspicion of tachycardiomyopathy (left ventricle dysfunction secondary to the tachycardia, which is reversible once controlled), young age, AF of recent apparition with data supporting the probability of maintaining sinus rhythm, and patients in which the rate control does not produce an adequate symptom management or adequate heart rate control.

In the majority of patients with heart failure and AF, the preferred initial strategy should be rate control

Rhythm control can reduce mortality

In none of the studies comparing the two strategies^{7,13-16} was there a reduction in mortality. In the AFFIRM study^{7,23,24} which included more than 4000 patients, mortality (primary endpoint) was greater in the case of rhythm control, although without statistical significance, 23.8% vs 21.3%, HR=0.87 (CI 95% 0.75-1.01). The subgroup of patients ≥ 65 years and the patients with no history of heart failure presented greater mortality in the case of rhythm control. Oral anticoagulation was associated with greater survival and better results in maintaining sinus rhythm, with no need to justify whether this was a determinant of survival or a marker of other factors related to survival. It is interpreted that the benefit of maintaining sinus rhythm is offset by the negative effects of antiarrhythmic agents, producing a neutral result.

From here the hypothesis is proposed, which up to now remains unconfirmed, that the most effective and safest methods to maintain sinus rhythm could be the favourable effect on survival. In the RACE trial¹³, the greater impact on the prognosis comes from the underlying heart disease and not from the therapeutic strategy or presence or not of AF. The meta-analyses²⁵⁻²⁷ of the studies that compare both strategies show that rate control is accompanied by a significant improvement in the composite endpoint of death and thromboembolism and a tendency of less mortality. In the AF and heart failure study, neither the rhythm control strategy nor success in maintaining sinus rhythm produced greater survival^{11,28}. In the RECORD AF registry²⁹, which included more than 5000 patients with paroxysmal or persistent AF of less than one year, the episodes depended on the co-morbidity but not on the management strategy. Lastly, in a meta-analysis of comparative studies with amiodarone vs other antiarrhythmic agents or placebo to study the efficacy in maintaining sinus rhythm, the possibilities of maintaining sinus rhythm was multiplied by three in the case of amiodarone, but there was no effect observed on mortality³⁰.

Why do we not obtain an improvement in survival out of rhythm control? As commented earlier, the negative effects of the antiarrhythmic agents, the conditioning of the underlying disease and the suboptimal efficacy of the methods employed to maintain sinus rhythm could explain these results.

In summary, the rhythm control strategy does not reduce mortality and the use of antiarrhythmic agents could increase it. It still remains a query whether the availability of more effective and safer methods to maintain sinus rhythm would produce a different result.

Rhythm control improves quality of life

In the AFFIRM study³¹⁻³² the quality of life was similar in both strategies, although patients who maintained AF status referred worse NYHA functional grades. Nor were there differences in cognitive function. In the 6-minute test, the rhythm control strategy showed a modest improvement of 10% with respect to the rate control group (they walked 28 metres more). In the PIAF study, whose primary endpoint was improvement in symptoms, there were no differences between both strategies. Neither did the RACE study³³ show differences in quality of life. This improvement was not related to the management strategy but to the presence of symptoms at the onset of the study, short lasting AF, and the presence of sinus rhythm at the end of the trial. Neither did a meta-analysis²⁷ show improvement in the quality of life, instead it showed an increase in hospital admissions and adverse effects in the rhythm control group.

However, in the J-Rhythm study³⁴, carried out in highly selected patients of Asian origin, with paroxysmal AF and a low proportion of structural heart disease, the primary composite endpoint (death, symptomatic stroke, embolism, major haemorrhage, and physical or mental disability) showed the superiority of the rhythm control strategy. This was because there were less treatment adjustments, which was associated with an improvement in some of the specific scales relevant to the evaluation of quality of life in AF (lower frequency in symptoms) while in others there was no improvement (severity of symptoms, anxiety, and daily task limitations). Both strategies improved quality of life.

Definitively, it is not clear whether rhythm control improves quality of life, as even the methodological studies are not highly refined. In any case, the possible improvement seems only modest and is limited by more hospital admissions and more adverse effects. Patients that could most benefit are those with symptomatic paroxysmal AF or AF with poor symptom control under a rate control strategy.

What does the current evidence have to say?

A synthesis of the main clinical trials can be found in table 3. Only one of the studies³⁴ showed superiority of a rhythm control strategy, at the expense of attaining less modifications in treatment, and improved quality of life of the patients with paroxysmal AF and low degree of structural cardiac disease. In the rest of the studies^{7,11,13-16} and meta-analyses^{19,25-27}, there were no significant differences between both strategies and there is concerning evidence of a possible increase in mortality in the rhythm control strategy, probably in relation with the use of antiarrhythmic drugs.

It also remains clear the importance of maintaining anticoagulation even in cases of achieving and maintaining sinus rhythm. In patients with heart failure and systolic dysfunction, rhythm control management was not superior¹¹. In any case, it should be made clear that the populations under study represent a group of patients with persistent AF and risk of embolism. The most important limitations would include:

- The results are not applicable to symptomatic paroxysmal AF.
- There are no data on young populations, the majority of which present AF with no structural heart disease or structural atrial remodelling.
- In the rhythm control strategy ablation has not been studied, a technique under study currently in various trials. In any case, ablation in AF is a complex procedure and presents greater risk of complications than other indications of ablation³⁵⁻³⁷. According to the European guidelines¹, the indication for ablation is justified when the “potential benefits are sufficient to justify the complicated procedure that can produce serious complications.” Moreover, it is a difficult technique to extend to a wide group of the population that presents AF. Until more information is available, the main indication for ablation is poor control of symptoms under pharmacological management.
- Some authors propose a different management option of the population where insufficient data are available and offer the hypothesis of superiority of rhythm control. These are patients with a first short lasting AF event, with no evidence of significant structural atrial remodelling in which the probabilities of maintaining sinus rhythm is higher, even when no antiarrhythmic agent is given³⁸⁻⁴¹.

The rhythm control approach does not reduce mortality and the use of antiarrhythmic drugs may rather increase it

What to do in clinical practice

The European AF registry^{42,43} shows that the frequency with which a rhythm control strategy is employed with regard to symptoms is alarming. In patients with asymptomatic AF, rhythm control was chosen in 44% of the cases, which increased to 67% when including symptomatic AF patients. Given that the absence of symptoms does not support this alternative, it is surprising to note that nearly half of the asymptomatic patients were under rhythm control management. In the international RECORD AF registry²⁹ which includes over 5000 patients followed up by cardiologists and diagnosed with non-permanent AF of less than one year, the rhythm control strategy does not seem coherent with the available evidence.

Despite the absence of evidence in favour of rhythm control and its inconveniences (hospital admissions, adverse effects, costs, etc.) in clinical practice this management option is employed in a considerably high percentage of patients with AF.

Does the use of dronedarone imply an advance in favour of the rhythm control strategy?

Dronedarone is a drug with a similar mechanism of action to amiodarone but with less adverse effects due to the absence of iodine and lower accumulation rates. Studies available show greater efficacy compared to placebo in the maintenance of sinus rhythm⁴⁴, but clearly inferior to amiodarone, although with less adverse effects reported^{45,46}. The ATHENA study⁴⁷ carried out in over 4000 patients with paroxysmal or persistent AF showed superiority in comparison to placebo with regard to the primary endpoint (mortality or hospital admission due to AF). In fact, the approved indication by the FDA is to reduce the need for hospital admissions in cases of paroxysmal or permanent AF. This does not correspond to a hard out-

come and could vary according to setting, health system structure, etc.

Moreover, the safety of the drug is questionable. The ANDROMEDA trial⁴⁸ carried out on patients admitted for heart failure and severe systolic dysfunction was discontinued early due to an increase in mortality. Recently the PALLAS trial⁴⁸ carried out in patients with permanent AF with high cardiovascular risk was also stopped early due to an increase in cardiovascular events (the risk of mortality, stroke, and heart failure hospital admission was increased twofold). The EMA⁴⁹ recommends restricting its use and not employing it in cases of permanent AF, heart failure, or systolic dysfunction. Moreover, an increase in adverse effects affecting the liver, lung and cardiovascular system was observed and requiring vigilance.

Dronedronone is not a therapeutic advance in the management of AF given its low efficacy in maintaining sinus rhythm, the scarce relevance of the clinical benefits, and the safety issues and adverse effects yet to be clarified.

The use of antiarrhythmic agents to maintain sinus rhythm⁵⁰⁻⁵¹

Success in the rhythm strategy control requires the use of antiarrhythmic drugs. However, this group of drugs presents important limitations in regard to efficacy and safety. The main drugs, ordered from more to less efficacy are: amiodarone, group IIB antiarrhythmic agents (flecainide and propafenone), sotalol, and in last place dronedarone.

With regard to safety, amiodarone is the only drug that can be employed in the presence of significant structural heart disease though the rate of withdrawals due to adverse effects is rather high. In the previous section there is an indication to the existing hesitation to use dronedarone. Flecainide and propafenone should not be employed in the presence of ischemic heart disease or significant structural heart disease. Compared to placebo, all these agents present a higher rate of adverse effects that lead to suspension in their use and all, except for amiodarone and propafenone have presented proarrhythmic effects in studies with patients with AF. It remains unclear whether long-term benefits are greater than the risk incurred. Table 4 indicates a proposal for selecting an antiarrhythmic drug on the basis of the underlying heart disease.

Oral flecainide or propafenone in high single doses are employed for the out-patient treatment of recent-onset AF with the pill-in-the-pocket approach⁵². Before indicating this option the efficacy

and safety should be tested under heart monitoring conditions.

Therefore, the efficacy of the antiarrhythmic agents is limited and its use is not free of adverse effects which in occasions may prove severe. It is important to select the most appropriate drug according to the characteristics of the patient and check for adverse effects.

Ablation in AF¹

This procedure consists of isolating pulmonary veins and their entrance point at the atrium from the rest of the left atrium. The majority of procedures are carried out with percutaneously via catheters (less frequent with surgery) employing radiofrequency as the energy source (although there are other alternative sources). Compared to well established ablations, this procedure is laborious and complex, less effective and may present greater risk of severe complications and more frequent recurrences.

The majority of the studies have been carried out by experienced doctors in patients with symptomatic paroxysmal AF and no or minimum structural heart disease. The success of the procedure after nearly one year is about 80% in the case of paroxysmal AF and 70% in persistent AF. A third of the patients require antiarrhythmic drugs and it is not uncommon that the procedure needs to be repeated^{53,54}. In 4% of the cases, severe complications related to the procedure occur. Long-term recurrences (4-5 years) range between 25-40%, which raises questions about the "curative" properties of the procedure^{55,56}. On the other hand, different studies show that ablation is superior to antiarrhythmic drugs in maintaining sinus rhythm in paroxysmal AF¹. There is a lack of data to better establish its role in persistent AF and in patients with AF and heart failure. Nor is there information on mortality and it is an error to consider ablation as a method to avoid anticoagulation.

Before opting for ablation, it is important to consider the patient's age, symptoms, alternative management options, left atrium "damage" (history and AF type, atrium size), structural heart disease and the experience of the doctors that will carry out the procedure. There should be a potentially sufficient benefit expected to justify a complex procedure not free of the risk of severe complications¹.

Ablation should be reserved for symptomatic patients, especially those with paroxysmal AF, despite appropriate medical treatment for rate and rhythm control.

The young patient^{1,57-59}

In young patients it is frequent to find different forms of AF including “isolated” AF (with no cardiopulmonary disease or other diseases such as arterial hypertension or diabetes), sports endurance and family related AF, which are characterized by the absence of structural heart disease, “normal” left atrium, low embolism risk and higher probability of maintaining sinus rhythm.

This population is poorly represented in studies that compare rate and rhythm control strategies, and so conclusions from these studies cannot be extrapolated to young people. In this population, although not demonstrated, it seems reasonable to adopt predominantly a rhythm control approach. Moreover the prolonged use of some antiarrhythmic drugs such as amiodarone is not advised and the use of ablation could have a wider indication^{1,60}.

In young people focal AF is most frequent⁶¹, which originates at ectopic foci at the entrance of the pulmonary veins in the left atrium. Suspicion can be made from EKG presenting auricular extrasystoles, sometimes in paroxysms or runs of atrial tachycardia or AF intercalated with wide wave AF. Ablation could be especially useful in these cases. Although uncommon, young patients with no apparent structural heart disease should be studied for channel abnormalities (Brugada, long QT or short QT syndromes) which are mutations in the ion transport channels related to severe arrhythmias, which can be triggered off by antiarrhythmic drugs. In table 5 there is a list of disorders to rule out in studies of AF in young patients and the relevant diagnostic studies.

Management of AF in young patients should be carefully planned on an individual basis. The management strategy to be employed will most commonly be rhythm control, but symptoms, adverse effects of antiarrhythmic drugs and local results of ablation should be considered.

What do the guidelines say?

The European guidelines¹ propose a complex plan in which the rhythm control approach is indicated in three different groups (class I-IIa recommendation, B-C level of evidence):

- Patients with poor symptom management under rate control treatment.
- Young patients.
- Patients with paroxysmal AF, especially when symptomatic and with no structural heart disease.

In clinical practice rhythm control strategy is widely employed without justification

The indication of ablation is generally reserved for patients that are symptomatic despite optimum medical treatment (class IIa-IIb recommendation, level of evidence A-C).

The American guidelines³ do not offer a clear and specific decision plan on what strategy to employ. Just like the European guidelines, they also incorporate ablation of AF within the rhythm control strategy. Neither do the Canadian guidelines propose a decision plan and recommend the rhythm control strategy depending on the patient’s symptoms and preferences. They enumerate a series of factors that may influence the decision on the choice of strategy to employ: type of AF, symptoms, age, etc. They also incorporate ablation in AF in patients who do not respond to pharmacological management.

Practical recommendations in choosing the most appropriate approach

The most important factors to bear in mind are:

Symptom control. When adequate management is achieved with a rate control approach, then this should be continued. This is especially valid for aged patients, patients with persistent AF or with structural heart disease.

Dronedarone is not very effective in maintaining sinus rhythm and presents significant safety problems that have not been clarified as yet

Age. In young patients it is preferable to attempt a rhythm control approach, including ablation. In any case, management should be on an individual basis and should consider symptom control and probabilities of recurrence.

Duration of AF. In general, in the case of paroxysmal AF it is preferable to employ rhythm control strategy. In cases of persistent AF, the decision should be made considering symptoms, age and the probability of maintaining sinus rhythm.

Probability of recurrence of the arrhythmia. This factor is easy to identify in extreme situations but difficult to spot in the rest. The possibilities of maintaining sinus rhythm are maximum in AF due to a process that has been resolved, and in recent AF with normal left atrium or mildly dilated and no evidence of arterial hypertension, heart failure or structural heart disease.

Safety. This factor should be present when deciding on employing antiarrhythmic drugs, just like the case of ablation.

Preferences of the well-informed patient given the options available.

In any case, it should be noted that rate or rhythm control strategies are not opposed but complementary, and in the course of AF, a change in strategy may be necessary. According to our criteria, the majority of patients with AF are candidates for an initial rate control strategy and oral anticoagulation, while a rhythm control approach should be considered in the following cases:

- Poor symptom control.
- Poor rate control (risk of tachycardiomyopathy).
- Young patients.
- AF of recent onset with low risk of recurrence.
- Clear preference of the well informed patient.

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Conclusions

The choice between rate or rhythm control is not the most important decision in the management of AF and these strategies should be considered more as complementary rather than antagonistic.

The rhythm control approach has not proved superior to rate control with regard to either mortality or the incidence of stroke or embolism or improvements in progress to heart failure. The benefits on the quality of life are not clear and this approach can produce adverse effects and higher hospital admissions.

In the majority of the population with AF, rate control is the elective choice.

The data available shows an excessive use of rhythm control in clinical practice.

The choice of a rhythm control approach should be on the basis of rate control (symptoms and poor rate control), young age, the identification of patients with a low risk of recurrence and the presence of AF secondary to a reversible process.

When deciding on a rhythm control then precaution should be taken by considering adverse effects, choosing an adequate drug and carefully selecting candidates for ablation.

Table 1. Stratification of embolism risk. CHADS2 score.

ACRONYM	DEFINITION	SCORE	RECOMENDATION ACCORDING TO SCORE
C	Heart failure	1	Aspirin or no treatment OAC o aspirin (preferably OAC) ≥2 OAC
H	Arterial hypertension	1	
A	Age ≥ 75 years	1	
D	Diabetes	1	
S2	Stroke or embolism	2	

OAC = Oral AntiCoagulation.

Table 2. Stratification of embolism risk. CHA2DS2-VASc score.

ACRONYM	DEFINITION	SCORE	RECOMENDATION ACCORDING TO SCORE
C	Heart failure or EF ≤ 40%	1	None or aspirin (preferably no treatment) OAC or Aspirin (preferably OAC) ≥2 OAC
H	Arterial hypertension	1	
A2	Age ≥ 75 years	2	
D	Diabetes	1	
S2	Stroke or embolism	2	
V	Vascular disease	1	
A	Age 65-74 years	1	
Sc	Women	1	

OAC = Oral Anticoagulation. Vascular disease = myocardial infarction, peripheral arterial disease or complex plaques in the aorta. EF = ejection fraction.

Table 3. Clinical Studies of rate and rhythm control in AF (1).

STUDY (YEAR)	No PATIENTS	AVERAGE AGE (YEARS)	AVERAGE FOLLOW-UP (YEARS)	INCLUSION CRITERIA	PRIMARY ENDPOINT (PE)	RESULTS OF PE (%)		
						RATE CONTROL	RHYTHM CONTROL	p
PIAF (2000)	252	61	1	Persistent AF	Improved symptoms	60.8	55.1	0.32
AFFIRM (2002)	4060	69.7	3.5	AF or persistent, ≥ 65 years, risk of stroke, or death	Death	25.9	26.7	0.08
RACE (2002)	522	68	2.3	Persistent AF or flutter of < 1 year and 1-2 cardioversions in 2 years and OAC	CV death, severe hemorrhage, pacemaker, embolism, severe effects of antiarrhythmic drug	17.2	22.6	0.11
STAF (2003)	200	66	1,6	Persistent AF of <2 years, LA > 45 mm, HF NYHA II-IV, EF < 45%	Death. Cerebrovascular complications, CPR, embolism	10	9	0.99
HOT CAFÉ (2004)	205	60.8	1.7	Persistent AF of < 2 years, 50-75 years	Embolism, Severe or intracranial hemorrhage	1	3.9	>0.71
AF-CHF (2008)	1376	66	3.1	EF ≤ 35%, symptoms of HF, history of AF in last 6 months	CV death	25	27	0.59
J-RHYTHM (2009)	823	64.7	1.6	PAF	Death, symptomatic stroke, embolism, severe bleeding, physical or psychological disability	22	15.3	0.012

OAC: oral anticoagulation; AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management; LA: Left atrium; AF: atrial fibrillation; PAF: paroxysmal atrial fibrillation. EF: left ventricle ejection fraction; HOT CAFÉ: How to Treat Chronic Atrial Fibrillation; HF: heart failure; J-RHYTHM: Japanese Rhythm Management Trial for Atrial Fibrillation; NYHA: New York Heart Association; PIAF: Pharmacological Intervention in Atrial Fibrillation; RACE: RATE Control versus Electrical cardioversion for persistent atrial fibrillation; CPR: cardiopulmonary resuscitation; STAF: Strategies of Treatment of Atrial Fibrillation.

Table 4. Choice of antiarrhythmic drug to maintain sinus rhythm.

NO STRUCTURAL HEART DISEASE (OR MILD HEART DISEASE)	WITH STRUCTURAL HEART DISEASE
No structural heart disease (or mild heart disease) First Choice: flecainide, propafenone, sotalol Second alternative: dronedarone* Third alternative: amiodarone	LVH: Dronedarone* (amiodarone as second choice) Coronary disease: sotalol, dronedarone* (amiodarone as second choice) Heart failure: amiodarone

(*) With regard to dronedarone there is still little experience and its role is not clearly established.

Table 5. AF in young patients. Factors to consider.

PROCESSES	INITIAL STUDIES
Structural heart disease Lung disease Family related AF Channel related diseases Thyroid dysfunction Others: arterial hypertension, diabetes, tobacco, renal failure, alcohol, obesity, athletes or vigorous exercise, subclinical atherosclerosis	Clinical history, EKG, ecocardiograph Clinical history, chest X-ray, stress tests, sleep studies Family history Family history, EKG Thyroid hormones

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