Atrial fibrillation: the rate versus rhythm management controversy

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ABSTRACT The fundamental management strategy for atrial fibrillation (AF) is still debated. There is no doubt that those patients at risk of thromboembolic events should be offered anticoagulant therapy. However, it is uncertain whether rhythm control (restoration and maintenance of sinus rhythm) or rate control (adjustment to a physiological ventricular rate while allowing AF to continue) is the preferred primary treatment option for the reduction of symptoms and major cardiovascular (CV) outcomes associated with AF.

Several well conducted trials comparing the two strategies led to the conclusion that there was little to choose between them. However, guidelines leaned towards recommending rate control as the initial strategy, and reserved rhythm control for those who remained symptomatic. Recently this status quo is being increasingly challenged by the clear demonstration that left atrial catheter ablation is effective at suppressing AF resistant to traditional antiarrhythmic drugs, such as those that failed to demonstrate any superiority when compared with rate control. Also, recently introduced antiarrhythmic therapy may have superior efficacy with regard to reducing unexpected CV hospitalization, CV mortality and stroke. In addition, there is a growing perception that atrial remodelling should be best prevented by early rhythm control rather than delaying until rate control has proven unsatisfactory.

For these reasons the results of large randomised clinical trials, which recruit patients soon after the presentation of AF and compare 'aggressive' modern rhythm control against the guideline approach of primary rate control, are eagerly awaited. In the meantime the pendulum of clinical opinion has begun to swing towards a rhythm control strategy.

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INTRODUCTION

Atrial fibrillation (AF) is an increasingly prevalent arrhythmia, affecting close to 2% of the general population.[1,2] It accounts directly for over 15% of all strokes; many cryptogenic strokes may also be due to this arrhythmia.[3,4] Hospitalizations for the management of AF itself, acute coronary syndrome and for heart failure are increased when AF is present.[5–7] Exercise tolerance is generally reduced and quality of life is impaired, especially in symptomatic patients.[8,9]

AF occurs in conjunction with almost every cardiac or vascular disease and may also complicate diseases of the chest.[10] It may result from aging alone; most of the patients with this arrhythmia are relatively old and have underlying cardiac or pulmonary pathology. In younger patients, structural congenital cardiac disease or an association with channelopathies (QT abnormalities and Brugada syndrome), or familial cardiomyopathy (e.g. hypertrophic cardiomyopathy) may be responsible.[11] The majority of younger patients however have no apparent cardiovascular cause for their AF, other than mild hypertension (without left ventricular hypertrophy) or possible cardiac autonomic dysfunction. Other elements may also be responsible for the arrhythmia, including genetic factors,[11] a history of an inflammatory illness preceding the first episode, or toxic causes (e.g. alcohol, thyroid conditions, etc.).

While elderly patients, especially when sedentary and inactive, may be relatively asymptomatic from AF, younger patients (who are usually more active) find AF to be a very symptomatic and debilitating disease.[12] Older patients may blame their symptoms on 'getting old' and accommodate by lowering their expectations and adjusting their lifestyle to the limitations imposed by the disease. Younger patients tend to expect a full eradication of the disease or at least complete suppression of their symptoms.

AF is typically divided into three types (paroxysmal, persistent and permanent) based on its presentation, duration, and response to therapy (if applicable).[13] Paroxysmal AF is a self-terminating arrhythmia; although the duration of paroxysms may vary greatly (with the upper limit arbitrarily set at seven days) the majority will end within 48 hours. The 48-hour time period is clinically important because after this the likelihood of spontaneous conversion is low and anticoagulation must be considered prior to any attempt to cardiovert the arrhythmia, irrespective of the underlying thrombo-embolic risk profile. If AF lasts longer than seven days or requires pharmacological or electrical cardioversion, it is referred as persistent. When AF does not convert spontaneously and is refractory to cardioversion or other rhythm control interventions, or if the physician or the patient chooses not to pursue the rhythm control strategy and allow AF to remain, the term permanent ('accepted') AF is applied. AF lasting more than one year (or six months according to recent statements from regulatory authorities (MULTAQ) is deemed to be 'permanent' but if a rhythm control strategy is to be pursued with cardioversion or catheter ablation the AF may be designated as 'long-standing persistent'.

When AF is first detected, it may be a single non-recurrent event secondary to a reversible or transient cause, or it may evolve into recurrent paroxysmal or persistent AF. The onset of AF however may be asymptomatic and the first detected episode should not be regarded as necessarily the true onset of the arrhythmia. AF episodes may or may not terminate spontaneously. There is usually a progression of the disease from paroxysmal to persistent and eventually permanent (or accepted) AF.[14] Progression from first diagnosed or recurrent paroxysmal AF to persistent or permanent AF occurs on average at the rate of 5% to 15% per year, depending on a number of factors, such as age at presentation and the presence of underlying heart disease (Table 1).[15]

RATE VERSUS RHYTHM CONTROL STRATEGIES

AF is due to very rapid atrial excitations, caused and sustained by a combination of re-entry and automaticity mechanisms,[16] which effectively paralyze atrial mechanical function. These excitations are conducted (to a limited extent) to the ventricles and induce a rapid and irregular ventricular rate response. There are two fundamentally different clinical approaches to the arrhythmia:[13]

Rate control: Slowing the ventricular rate to a level which is physiologically appropriate. It is not clear exactly what this rate should be, but most clinicians settle for rates at rest below 100 beats per minute. In clinical trials specific definitions have been applied.

Rhythm control: Suppressing the rapid excitation of the atrium and restoring sinus rhythm. Antiarrhythmic drugs (ion channel blockers) are most commonly used for this purpose, but occasionally autonomic manipulation, with beta blockers for example, may also prove effective. Successful rhythm control may eliminate or reduce recurrent AF or slow its progression.

Patients who are not severely symptomatic could be considered for treatment using either strategy. Both patients and physicians have taken part in clinical trials in which these patients were randomised to receive either rate control or rhythm control treatment. Patients who have severe and disabling symptoms often demand a more aggressive approach towards restoring and maintaining sinus rhythm; rate versus rhythm control trials would therefore be difficult, and have never been undertaken.

Rhythm control appears to be a more attractive treatment option, as it offers physiologic rate control, normal atrial activation and contraction, the correct sequence of atrioventricular (AV) activation and normal haemodynamic and AV valve function. It also theoretically eliminates one (stasis) or more (endothelial abnormality or increased thrombogenic blood constituents) of Virchow's triad of elements that encourage thrombosis within the atria and embolization of blood clots to potentially critical parts of the circulation. Advantages of the rate control approach on the other hand include avoiding the potential toxicity of antiarrhythmic drugs or the risks and discomfort associated with electrical cardioversion or invasive left atrial ablation for recurrences of AF.

Sinus rhythm with normal AV conduction may however not be an alternative treatment for AF since sinus node disease may be the underlying problem and chronotropic incompetence may be present. Atrial conduction and mechanical function may be seriously impaired due to existing AF, or underlying pathophysiologies such as left ventricular (LV) cavity dilatation, LV hypertrophy, hypertension, mitral valve disease, etc. Atrial contraction may not contribute much to cardiac output. AV conduction may be impaired because of associated structural disease, channelopathy or antiarrhythmic drug therapy. AV valve function may be structurally abnormal or functionally disturbed on a permanent basis because of dilatation of the atrium and AV valve annulus. AF which is not fully suppressed is likely to cause some symptoms which, when contrasted to asymptomatic periods of sinus rhythm, may make intermittent AF more troublesome than sustained AF.

It is not unusual for patients to be relieved of their symptoms when AF is established and becomes permanent. Often the only symptoms that remain are a minor limitation to exercise tolerance and a subtle

TABLE 1 Rates of progression of paroxysmal atrial fibrillation to persistent or permanent atrial fibrillation.

Study	Number of patients	Age, years	Type of AF	Follow-up, years	Progression of AF, %	Predictors of progression (risk)
European Heart Survey, 2010	1219	64 ± 13	Paroxysmal; lone AF: 17%	1	15 Permanent: 8 In subgroup with lone AF: 7 (persistent or permanent)	Age > 75 years (1.57), heart failure (2.22), hypertension (1.52), stroke/TIA (2.02), COPD (1.51)
RECORD-AF, 2011	2137	65.1 ± 12	Recent onset paroxysmal	1	15 Permanent: 9	Heart failure (2.2), hypertension (1.5), rate control (3.2) In subgroup with rhythm control as the initial strategy: heart failure (1.9), hypertension (1.8), heart rate (1.01)
Sakamoto (Tokyo), 1995	137	No progression: 62.4 ± 11 With progression: 70.1 ± 8.2	First detected paroxysmal	1	Sustained AF ≥ 6 months: 22	Age ≥ 65 years, heart failure, CTR ≥ 50%, diabetes, LA ≥ 38 mm, LVEF ≤ 0.76, f waves in V_1 ≥ 2 mm
Abe (Osaka), 1997	122	61 ± 12	Paroxysmal; lone AF: 21%	2.16	Sustained AF ≥ 6 months: 11.5	LA size, abnormal P-signal[c]-averaged ECG
Fauchier (Tours), 2010	2167	71 ± 14	Paroxysmal	2.6	14.1	Age > 75 years, heart failure, hypertension, COPD, number of electrical cardioversions, dilated cardiomyopathy, prosthetic valve
UK GPRD, 2005	418	Men: 67 ± 11, Women: 73 ± 10	First detected paroxysmal; no co-morbidity: 32%	2.7	11 at 1 year 17 at 2.7 years	Valvular heart disease (2.7), moderate to high alcohol intake (3.0)
Al-Khatib (Durham), 2010	231	60 ± 13	Paroxysmal; lone AF: 41.6%	4	8 at 1 year 18 at 4 years	Age (1.82 per decade), AF at presentation (3.56)
Pappone (Milan), 2008	106	57.5 ± 11.5	First detected paroxysmal; lone AF: 51%	5	Recurrent paroxysmal: 52.8 Persistent: 53.3[a] Permanent: 35.5[a] In subgroup with lone AF: 3.7 (persistent), 1.8 (permanent)	Age (1.19), heart failure (11.2), diabetes (17.3), drug therapy vs ablation
Rostagno (Florence), 1995	106	63 ± 11	First detected paroxysmal lone AF	6	Recurrent paroxysmal: 55.6 Sustained: 4.7%	–
Takahashi (Tokyo), 1980	94	60	First detected paroxysmal; lone AF: 24.5%	> 6	Sustained AF ≥ 6 months: 20.2–25.3	Rheumatic valvular disease; frequency of paroxysms

TABLE 1 (continued) Rates of progression of paroxysmal atrial fibrillation to persistent or permanent atrial fibrillation.

Study	Number of patients	Age, years	Type of AF	Follow-up, years	Progression of AF, %	Predictors of progression (risk)
CARAF, 2005	757	64 (median)	First detected paroxysmal	8	8.6 at 1 year 24.7 at 5 years Any recurrent AF: 63.2 at 5 years	Age (1.4 per decade), cardiomyopathy (2.41), aortic stenosis (3.04), mitral regurgitation (1.69), LA enlargement (3.05–4.17)
Danish Study, 1986	426	66 (median)	Paroxysmal	9 (median)	33.1	Underlying heart disease, thromboembolism
Kato (Tokyo), 2004	171	58.3 ± 11.8	First detected, paroxysmal	14	57 at 10 years 77 at 15 years	Age (1.27 per decade), myocardial infarction (2.33), valvular heart disease (2.29), LA enlargement (1.39)
Olmsted County, 1987	88	44	Lone AF	14.8	Recurrent paroxysmal: 58 Sustained: 12	–
Olmsted County, 2007	71	44.2 ± 11.7	Lone AF: 48% paroxysmal, 52% persistent	25.2	31 (30-year probability: 29)[b]	Age (1.7 per decade), QRS abnormalities (3.2)[d]

Abbreviations: **AF** = atrial fibrillation; **CARAF** = Canadian Registry of Atrial Fibrillation; **COPD** = chronic obstructive pulmonary disease; **CTR** = cardiothoracic ratio; **ECG** = electrocardiogram; **GPRD** = General Practice Research Database; **LA** = left atrium; **LVEF** = left ventricular ejection fraction; **TIA** = transient ischemic attack; [a] in patients on antiarrhythmic drugs (n = 45); [b] in the majority of patients within 15 years; [c] filtered P wave duration ≥ 145 ms and the root-mean-square voltage of the last 30 ms of the filtered P wave < 3 μV; [d] QRS ≥ 110 ms, QRS notching, small R in the precordial lead
Source: Savelieva et al.[15]

reduction of quality of life. Therefore there has been equipoise as to whether it is best to accept the arrhythmia while controlling the ventricular rate and preventing thromboembolic complications with anticoagulant therapy, or to restore and maintain sinus rhythm, and of course maintain anticoagulant therapy since it is likely that there will be unpredictable recurrences.

The difficulties in rhythm control management, principally the high AF recurrence rate and concern about the serious adverse effects associated with antiarrhythmic drug therapy, led to rate versus rhythm control studies.

THE RATE VERSUS RHYTHM CONTROL TRIALS

The Atrial Fibrillation Follow up Investigation of Rhythm Management (AFFIRM) trial, the RAte Control versus Electrical cardioversion (RACE) trial, and most recently the Atrial Fibrillation Congestive Heart Failure (AF CHF) trial are the major studies in this area [15,17,18] (Table 2). There have also been a series of small or pilot studies, including the Pharmacological Intervention in Atrial Fibrillation (PIAF), Strategies of Treatment of Atrial Fibrillation (STAF), and How tO Treat Chronic Atrial Fibrillation (HOT CAFÉ) among others.[18–20]

All of these randomised clinical trials directly and prospectively compared the effects of rhythm control treatment strategies with rate control strategies on a variety of endpoints ranging from exercise tolerance to all-cause mortality. Generally, no consistent differences between the strategies have been demonstrated, except for more hospitalizations and the costs associated with rhythm control. However the trials highlighted a trend toward improved survival and less serious cardiovascular adverse events in patients treated with a rate rather than rhythm control strategy.

The AFFIRM study of 4060 AF patients aged 65 years or older, with at least one risk factor for stroke, was the only trial designed to assess, as a primary endpoint, all-cause mortality benefit from these different strategies for AF management.[21] The mean follow-up was 3.5 years, with a maximum of six years. There was no difference in the primary endpoint of all-cause mortality or quality of life and functional status between rate and rhythm control.

TABLE 2 Clinical outcomes in rhythm versus rate control studies.

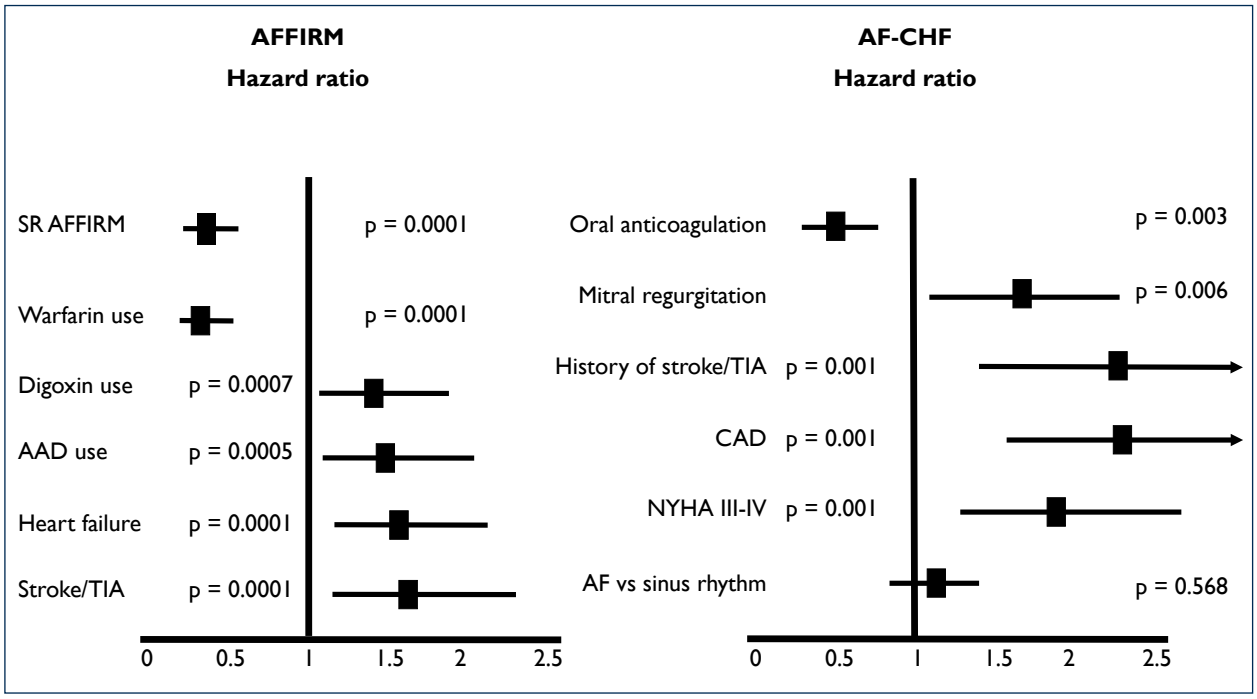
Study	PIAF	STAF	HOT CAFE	RACE	AFFIRM	AF-CHF	CRRAFT	J-RHYTHM
Number of patients	252	200	205	522	4060	1376	144	823
Follow-up, years	1	1.6	1.7	2.3	3.5	3.1	1	1.6
Primary endpoint	Symptom improvement	ACM, CV events, CPR, TE	ACM, TE, bleeding	CV death, hospitalization for CHF, TE, bleeding, pacemaker, AAD adverse effects	ACM	CV mortality	Clinical improvement	ACM, TE, bleeding, hospitalization for CHF, adverse effects
Difference in primary endpoint RhyC vs RC	Symptoms improved in 70 vs 76 pts (p=0.317)	5.54%/yr vs 6.09%/yr (p=0.99)	No difference (OR, 1.98; 95% CI, 0.28–22.3; p >0.71)	22.6% vs 17.2% (HR, 0.73; 90% CI, 0.53–1.01; p=0.11)	23.8% vs 21.3% (HR, 1.15; 95% CI, 0.99–1.34; p=0.08)	27% vs 25% (HR, 1.06; 95% CI, 0.86–1.3; p=0.59)	Significant improvement with RhyC	15.3% vs 22% (p=0.0128)
ACM RhyC vs RC	Not assessed	2.5%/yr vs 4.9%/yr	3 (2.9%) vs 1 (1%)	6.8% vs 7%	As above	32% vs 33% (p=0.68)	0 vs 5 (p=0.023)	4 (1%) vs 3 (0.7%)
TE RhyC vs RC	Not assessed	3.1%/yr vs 0.6%/yr	3 (2.9%) vs 1 (1%)	7.9% vs 5.5% RhyC vs RC	Stroke: 7.1% vs 5.5% (p=0.79)	3% vs 4% (p=0.32)	1 vs 0	2.39% vs 2.97%
CHF RhyC vs RC	Not assessed	Better with RC	No difference	4.5% vs 3.5%	2.7% vs 2.1% (p=0.58)	28% vs 31% (p=0.17)	Functional class improved in 60% vs 17.5% (p=0.0014)	0.5% vs 1.5%
Hospitalisation RhyC vs RC	69% vs 24% (p=0.001)[a]	54% vs 26% (p <0.001)	74% vs 12% (p <0.001)	More in RhyC	80% vs 73% (p <0.001)[a]	46% vs 39% (p=0.0063)	8.9% vs 15% (p=0.51)	Not reported
QoL RhyC vs RC	No difference	No difference	Not reported	No difference	No difference	Not yet available	Improved in 86.7% vs 50% (p=0.033)	Better with RhyC

Abbreviations: **AAD** = antiarrhythmic drugs; **ACM** = all-cause mortality; **AF** = atrial fibrillation; **AF-CHF** = Atrial Fibrillation and Congestive Heart Failure; **AFFIRM** = Atrial Fibrillation Follow-up Investigation of Rhythm Management; **CHF** = congestive heart failure; **CI** = confidence intervals; **CPR** = cardiopulmonary resuscitation; **CRRAFT** = Control of rate versus rhythm in rheumatic study in Rheumatic Atrial FibrillAtion Trial; **CV** = cardiovascular; **HOT CAFÉ** = HOw to Treat Chronic Atrial Fibrillation; **HR** = hazard ratio; **OR** = odds ratio; **PIAF** = Pharmacological Intervention in Atrial Fibrillation; **QoL** = quality of life; **RACE** = Rate Control versus Electrical Cardioversion; **RC** = rate control; **RhyC** = rhythm control; **RR** = relative risk; **STAF** = Strategies of Treatment of Atrial Fibrillation; **TE** = thromboembolic event; [a] = including hospitalization for cardioversion
Source: Savelieva et al[49]

However, this and other trials did not include younger, active or highly symptomatic patients, initial rate control could not have been easily applied to their management.

Post hoc analysis of the AFFIRM trial, after correction for any mismatch of baseline characteristics, has demonstrated that being in sinus rhythm was an advantage, but that the use of the then available antiarrhythmic drugs was associated with an increased risk of death.[22]

In the AF-CHF trial, rate and rhythm control strategies were compared specifically in 1376 patients with an ejection fraction of 35% or less and a New York Heart Association (NYHA) classification of II to IV heart



Abbreviations: **AAD** = antiarrhythmic drugs; **AF** = atrial fibrillation; **CAD** = coronary artery disease **NYHA** = New York Heart Association; **SR** = sinus rhythm; **TIA** = transient ischemic attack

FIGURE 1 Sub group analyses of AFFIRM and RACE illustrating discrepant results with regard to the presence of sinus rhythm

failure.[23] Amiodarone was the drug of choice (used in 82% of cases) for AF suppression and sinus rhythm maintenance, but sotalol and dofetilide were also used in select cases. The study showed no benefit to using rhythm control in addition to optimal medical therapy with regard to the primary endpoint (cardiovascular mortality) and pre-specified secondary endpoints (including total mortality, worsening heart failure, stroke, and hospitalization). Rhythm management was also found to be more expensive than rate control. Unlike the AFFIRM trial, the results of the AF-CHF trial did not confirm an advantage to using sinus rhythm in treating a population of elderly patients with heart failure (Figure 1).[24]

The similar primary endpoint results from using the rhythm and rate control strategies may have been due to a general failure to achieve a clear difference with respect to rhythm and rate status in the two arms of the trials. Ideally the rhythm control arm should have included patients who were in sinus rhythm, whereas the rate control arm should have consisted mostly of patients in AF. This was not however typically the case; in the AFFIRM trial for example, only 60% of the rhythm control arm were maintained in sinus rhythm, while 40% of the rate control arm had reverted spontaneously to sinus rhythm.

The generally neutral results of the rate versus rhythm control trials were broadly accepted by the clinical community. They were interpreted to imply that rate control therapy should be the primary therapeutic option for patients with recurrent forms of AF.[25] The reasons for this are not entirely clear but mostly relate to a belief that rate control is logistically easier than rhythm control, to the well-documented reduction in hospitalizations associated with rate control, and to the trend towards better major cardiovascular outcomes in favour of rate control (seen particularly in the AFFIRM and RACE trials). There was therefore a major shift towards the use of rate control and this was reinforced by the guidelines from the ACC, AHA and ESC published in 2001 and 2006.[26,27] The advice from the 2006 guideline regarding rate versus rhythm control for patients with paroxysmal AF is summarised in Figure 2.

However, these interpretations (i.e. initial treatment with rate control agents and later, and therefore delayed, treatment with rhythm control drugs only if symptoms persisted) were not accepted by the arrhythmia and electrophysiology community who were treating younger, more symptomatic patients. This was primarily because these patients had not been included in the relevant trials, and also because the treatment of recurrent AF was beginning to change dramatically at that time. A new antiarrhythmic agent was about to emerge, paroxysmal AF and some persistent AF were increasingly treated with direct left atrial ablation (such as pulmonary vein isolation) and the idea that interventional treatment would be much more successful and might even be 'curative' if adopted early in the course of the disease was spreading.[28]

FIGURE 2 Illustration of the default 'rate control' strategy adopted in guidelines issued by professional societies.[45]

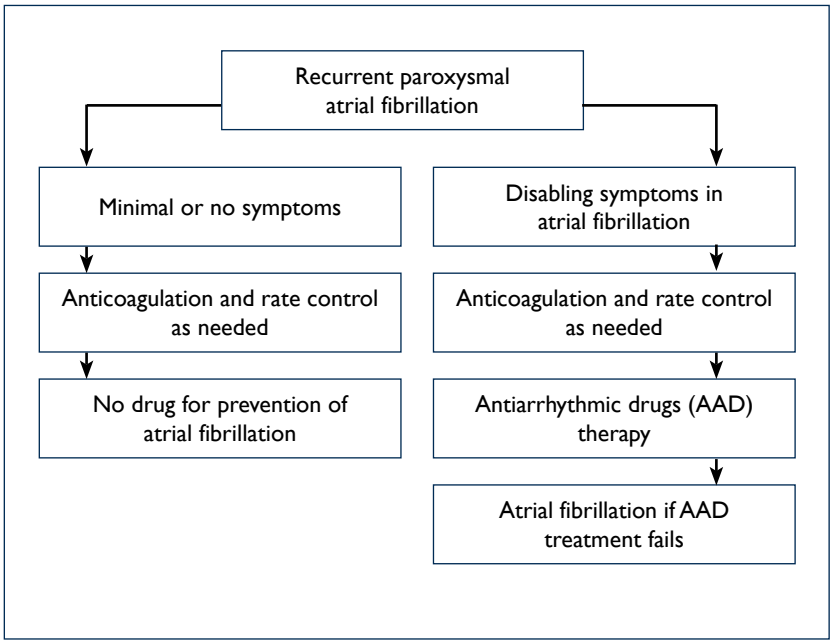


TABLE 3 Randomised controlled studies of pulmonary vein ablation versus antiarrhythmic drug therapy in atrial fibrillation.

Study	Number of patients	Type of AF	Previous use of AAD	Crossed to ablation in the ADD Group	AF free at one year	
					Ablation	AAD
Krittayaphong et al, 2003	30	Paroxysmal, persistent	≥1	Not stated	79%	40%
Wazni et al, 2005 (RAAFT)	70	Mainly paroxysmal	No	49%[a]	87%	37%
Stabile et al, 2005 (CACAF)	137	Paroxysmal, persistent	≥2	57%	56%	9%
Oral et al, 2006	146	Persistent	≥1 (mean 2.1 ± 1.2)	77%	74%	4%
Pappone et al, 2006 (APAF)	198	Paroxysmal	≥2 (mean 2 ± 1)	42%	86%	22%
Jais et al, 2008 (A4 study)	112	Paroxysmal	≥1	63%	89%	23%
Forleo et al, 2008	70	Paroxysmal, persistent	≥1	Not stated	80%	43%
Wilber et al, 2009 (Thermocool)	167	Paroxysmal	≥1 (mean 1.3)	59%[a]	66%	16%
Packer et al, 2010 (STOP-AF)	245	Paroxysmal	≥1	79%	69.9%	7.3%

Abbreviations: **AAD** = antiarrhythmic drugs; **AF** = atrial fibrillation; **APAF** = Ablation for Paroxysmal Atrial Fibrillation study; **A4** = Atrial fibrillation Ablation versus AntiArrhythmic drugs; **CACAF** = Catheter Ablation for the Cure of Atrial Fibrillation study; **RAAFT** = Radiofrequency Ablation Atrial Fibrillation Trial; **STOP-AF** = Sustained Treatment of Paroxysmal Atrial Fibrillation; [a] = after 1 year
Source: Camm AJ et al.[50]

TABLE 4 Long-term results of pulmonary vein ablation for atrial fibrillation

Study	Study type	Number of patients	Ablation strategy	Follow-up, months (±SD)	Arrhythmia free survival, %	Compli-cations, %
Gaita et al, 2008	Randomised 1:1 PVI vs. PVI + LL	204	PVI/PVI+LL	41.4 ± 6.2/ 39.7 ± 5.5	41	2
Fiala et al,2008	Randomised 1:1 segmental PVI vs circumferential PVI	110	PVI	48 ± 8	56	1
Bertaglia et al, 2009	Observational	177	PVI/PVI+LL	49.7 ± 13.3	58	Not reported
Bhargava et al, 2009	Observational	1404	PVI/PVI+LL	59 ± 16	73	3
Tsou et al, 2010*	Observational	123	PVI	71 ± 18	71	Not reported
Wokhlu et al, 2010	Observational	774	PVI/PVI+LL	36 ± 22.8	64	Not reported
Ouyang et al, 2010	Observational	161	PVI	57.6	47	2
Weerasooriya et al, 2011	Observational	100	PVI/PVI+LL	60	32	6

Abbreviations: **LL** = left lines; **PVI** = pulmonary vein isolation; **SD** = standard deviation
*only patients free from AF one year after ablation were included; in a total of 239 patients who underwent AF ablation, the success rate after 71 ± 18 months was only 36.4%

CURRENT STATUS OF RATE VERSUS RHYTHM STRATEGIES

The results of rate versus rhythm control studies highlighted the limitations of the therapies at that time to achieve and maintain sinus rhythm. Long-term maintenance of sinus rhythm has proven difficult to achieve in patients with persistent AF, and the strategy is time-consuming and expensive due to the costs of the antiarrhythmic drugs and the increased need for hospitalization. Little was known about the criteria for adequate and safe rate control.[29] A study from the AFFIRM database, and another comparing the results of AFFIRM (strict rate control) to RACE (lenient rate control) suggested that a lenient approach to rate control is at least as effective as a strict rate control procedure.[30] This conclusion was confirmed by a recent prospective randomised trial comparing strict control (<80 beats/minute at rest and <110 beats/minute on moderate exercise) with lenient control (<110 beats/minute at rest).[31] Strict rate control was associated with more bradycardia and pacemaker implantation. These developments imply that the therapeutic emphasis on rate control may be tempered or even reversed if safer and more effective rhythm control therapies were to become available.

The use of left atrial ablation to isolate triggers, most often by pulmonary vein isolation, and/or to break up the substrate for AF by creating lines of block or eradicating areas of critical slow conduction, have proved successful in reducing the recurrence of AF (Table 3).[32,33] This is particularly true in patients with paroxysmal AF of short duration, normal left atrial anatomy and size, and normal left ventricular function. The results with persistent AF, or with AF which would otherwise be designated as permanent, are also encouragingly positive, even when significant left ventricular systolic dysfunction is present.[34] Often more than one procedure is needed, particularly in the complex cases mentioned above.[35] There is also some concern about long-term recurrence which is now recognised to be about 5% per annum even in patients who remain arrhythmia-free for the first year or so.[36–38] The recurrences tend to be short in duration however and relatively infrequent. Further ablation procedures may be needed and are often successful (Table 4).

Dronedarone is a new antiarrhythmic drug, structurally similar to amiodarone, but it does not contain iodine and is not lipophilic.[39] Significant cutaneous or thyroid effects have not been seen. The electrophysiological spectrum of the drug also differs significantly from that of amiodarone – it is a more powerful sodium, calcium and acetylcholine-dependent K current (IKACh) blocker. This drug is an effective antiarrhythmic agent, also shown to reduce hospitalizations for AF and AF related co-morbidities, such as heart failure, and acute coronary syndrome in patients with recurrent forms of AF (Table 5).[40,41] Dronedarone, however, appears not to be safe to use in patients with severe heart failure[42] or permanent AF, especially in the presence of heart failure.[43] There is some concern over severe liver toxicity,[44] which has been

TABLE 5 Summary of clinical studies of dronedarone in atrial fibrillation.

Study	Number of patients	Patient character-istics	Dose of drone-darone	Placebo cont-rolled	Primary endpoint	Follow-up, months	Outcome of drone-darone vs placebo for amio-darone
DAFNE	199	Persistent AF post cardioversion	400 mg bid 600 mg bid 800 mg bid	Yes	Time to first AF recurrence	6	Median time to first AF recurrence on 400 mg bid: 60 vs 5.3 days (relative risk reduction, 55%; 95% CI, 28–72% p = 0.001) The effect was less apparent at higher doses Treatment discontinuation due to adverse effects: 3.9%, 7.6%, 22.6% on 400, 600, 800 bid. vs 0%
EURIDIS	615	Paroxysmal and persistent AF post cardioversion	400 mg bid	Yes	Time to first AF recurrence	12	Median time to first AF recurrence: 96 vs 41 days, p = 0.01
ADONIS	630	Paroxysmal and persistent AF post cardioversion	400 mg bid	Yes	Time to first AF recurrence	12	Median time to first AF recurrence: 158 vs 59 days, p = 0.002
EURIDIS and ADONIS combined	1237	Paroxysmal and persistent AF post cardioversion	400 mg bid	Yes	Time to first AF recurrence	12	Median time to first AF recurrence: 116 vs 53 days Recurrence at 12 months: 64.1% vs 75.2% (HR, 0.75; 95% CI, 0.65–0.87; p <0.001
EURIDIS and ADONIS post-hoc	1237	Paroxysmal and persistent AF post cardioversion	400 mg bid	Yes	All-cause mortality and hospitalization	12	All-cause mortality and hospitalizations: 22.8% vs 30.9% (HR, 0.73; 95% CI, 0.57– 0.93; p = 0.01)
ERATO	630	Permanent AF with ventricular rates >80 bpm on rate controlling therapy	400 mg bid	Yes	Mean 24-hour ventricular rate at 2 weeks	1	11.7 bpm lower on dronedarone (p <0.0001) 24.5 bpm lower on dronedarone during maximal exercise (p <0.0001)
ANDRO-MEDA	617	Congestive heart failure; EF <0.35	400 mg bid	Yes	All-cause mortality and hospitalization for heart failure	2 (median)	Stopped early because of excess mortality in the dronedarone arm: 8.1% vs 3.8% (HR, 2,13; 95% CI, 1.07–4.25; p = 0.03) Primary endpoint: 17.1% vs 12.6% (HR, 1.38; 95% CI, 0.92–2.09; p = 0.12)
ATHENA	4628	Paroxysmal or persistent AF with risk factors	400 mg bid	Yes	All-cause mortality and hospitalization for cardio-vascular events	1.7 (range, 1–2.5)	Primary endpoint: 31.9% vs 39.4% (HR, 0.76; 95% CI, 0.69–0.84; p <0.001) Hospitalization: 29.3% vs 36.9% (HR, 0.74; 95% CI, 0.67–0.82; p <0.001) All-cause mortality: 5% vs 6% (HR, 0.84; 95% cl, 0.66-1.08; p = 0.18)

Study	Number of patients	Patient characteristics	Dose of dronedarone	Placebo controlled	Primary endpoint	Follow-up, months	Outcome of dronedarone vs placebo for amiodarone
DIONYSOS	504	Persistent AF	400 mg bid	No; amiodarone used as an active comparator	AF recurrence (including unsuccessful direct current cardioversion [DCC]) or drug discontinuation; secondary safety endpoints	12 (median, 7)	Primary endpoint: 75.1% vs 58.8% (HR, 1.59; 95% CI 1.28–1.98; p <0.0001) AF recurrence: 36.5% vs 24.3% Main safety endpoint: 39.3% vs 44.5% (HR, 0.80; 95% CI, 0.60–1.07; p = 0.129)
PALLAS	3149	Permanent AF with risk factors	400 mg bid	Yes	MACE (cardiovascular death, myocardial infarction, stroke, systemic embolism) or unplanned cardiovascular hospitalization and all-cause mortality	12 (median, 7)	Stopped early because of excess co-primary endpoints in the dronedarone arm. Major adverse cardiac events (MACE): 2% vs 0.9% (HR, 2.3; p = 0.009) All-cause mortality and unplanned hospitalization: 7.5% vs 5.1% (HR, 1.5; p = 0.006) Death: 1% vs 0.4% (HR, 2.3; p = 0.065)

Abbreviations: **ADONIS** = American-Australian-African trial with DronedarONe In atrial fibrillation or flutter for the maintenance of Sinus rhythm; **AF** = atrial fibrillation; **ANDROMEDA** = ANtiarrhythmic trial with DROnedarone in Moderate to severe heart failure Evaluating morbidity DecreAse; **ATHENA** = A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter; **bpm** = beats per minute; **DAFNE** = Dronedarone Atrial FibrillatioN study after Electrical cardioversion; **DIONYSOS** = Double blind trlal to evaluate efficacy and safety of drOnedarone (400 mg bid) versus amiodaroNe (600 mg qd for 28 daYs, 200 mg qd thereafter) for at least six mOnths for the maintenance of Sinus rhythm in patients with atrial fibrillation; **EF** = ejection fraction; **ERATO** = Efficacy and Safety of Dronedarone for the Control of Ventricular Rate; **EURIDIS** = EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm; **PALLAS** = Permanent Atrial fibriLLation outcome Study

documented in rare cases but detailed post-approval studies have so far failed to confirm the concern. Unlike other drugs, dronedarone has not been associated with any pro-arrhythmia other than mild bradycardia.

Both dronedarone and left atrial ablation are recommended in recent guidelines for the management of patients with recurrent AF. The focused update incorporated into the ACC, AHA and HRS guidelines (2011)[45] give a class 1 level recommendation for ablation of paroxysmal AF in optimal circumstances, and the ESC guidelines (2010)[13] give a class 2a level recommendation for ablation of both paroxysmal and persistent AF and a 2b level recommendation for ablation of paroxysmal AF without the need to demonstrate failure with previous antiarrhythmic drug therapy. This guideline also supports (class 2b) ablation of AF in patients with systolic heart failure. Both guidelines recommend the use of dronedarone within its licensed indications. The ESC guideline no longer recommends that there should always be an attempt to control symptoms with rate control before considering the adoption of a rhythm control strategy. Early rhythm control may be important if the strategy is to stand any chance of long-term success.

New 'rate versus rhythm control' trials are urgently needed because younger, more active and more symptomatic patients should be studied. Better therapies than the older antiarrhythmic drugs used in the previous rate versus rhythm trials are now available. Left atrial ablation, and/or possibly dronedarone, might be used to provide safer and more effective rhythm control.
It is suggested that rhythm control should be timed much earlier during the course of the disease in order to prevent the progression of AF.[46] Left atrial ablation or antiarrhythmic agents might be used to isolate or suppress triggers of AF or modify the substrate for example. If given early in the course of the disease, before substantial atrial remodelling has taken place due to the AF itself ('AF begets AF') or due to the haemodynamic stress associated with underlying diseases such as hypertension and heart failure (which themselves can be aggressively managed), the recurrence of AF may be averted.[47] Such considerations are the basis

for large trials such as EAST (Early Atrial fibrillation Stroke Prevention Trial, NCT01288352) and CABANA (Catheter ABlation versus ANtiarrhythmic drug therapy for Atrial fibrillation, NCT00911508).[48]

CONCLUSIONS

For the majority of patients with recurrent AF there is abundant and largely consistent randomised clinical trial evidence that the best initial strategy is rate control; rhythm control should only be considered if symptoms remain troublesome. However, little or no such evidence exists in younger, active and highly symptomatic patients. There is good evidence that left atrial ablation is considerably better than conventional antiarrhythmic drug therapy for the prevention of paroxysmal AF recurrences, although no trials have yet investigated whether ablation techniques result in a long-term reduction of major cardiovascular outcomes. Nonetheless, the clinical pendulum of rate versus rhythm control is swinging towards rhythm control. Results from large scale randomised clinical trials are urgently needed to evaluate whether a rhythm control strategy in the modern era can surpass rate control in terms of slowing the progression of AF, improving quality of life, and reducing cardiovascular consequences, including mortality.

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