Rhythm *vs.* rate control of atrial fibrillation meta-analysed by number needed to treat

Cyrus R. Kumana, Bernard M. Y. Cheung, Giselle T. Y. Cheung, Tori Ovedal, Bjorn Pederson & Ian J. Lauder¹

Departments of Medicine and ¹Statistics and Actuarial Science, The University of Hong Kong, Hong Kong, SAR

Correspondence

Professor C.R. Kumana, Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong.
Tel: + 852 2855 4248
Fax: + 852 2855 1143
E-mail: hrmekcr@hkucc.hku.hk

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Background

Whenever feasible, rhythm control of atrial fibrillation (AF) was generally preferred over rate control, in the belief that it offered better symptomatic relief and quality of life, and eliminated the need for anticoagulation. However, recent trials appear to challenge these assumptions.

Aims

To explore the desirability of rhythm *vs.* rate control of AF by systematic review of pertinent, published, randomized controlled trials (RCTs) and a meta-analysis by number needed to treat (NNT) year⁻¹, with respect to diverse clinically important outcomes.

Methods

RCTs of outcome primarily comparing rate *vs.* rhythm control in patients with spontaneous AF were identified. For each outcome and assuming rhythm control to be the active treatment, relative risk reduction (RRR) and NNT year⁻¹ were derived for individual trials together with an NNT year⁻¹ for all trials combined; corresponding 95% confidence intervals (CI) were also calculated. Adverse drug reaction (ADR) and quality of life reporting were also assessed.

Results

In all, data from five suitable RCTs (entailing 5239 patients) were analysed. For hospitalization, available RRRs and NNT year⁻¹ values were all clinically and statistically significant. Overall, one additional patient was hospitalized for every 35 assigned to rhythm control (95% CI 27, 48). For the endpoints of death, 'ischaemic' stroke and 'non-CNS' bleeding, there was no significant difference. ADRs were significantly more common in rhythm control patients, whereas quality of life assessments revealed no difference. Thromboembolism was associated with cessation of or subtherapeutic anticoagulation, irrespective of treatment assignment.

Conclusion

Reduced risk of hospitalization and non-inferiority for other endpoints all favour rate control, the less costly strategy. If symptoms of AF are not a problem, treatment should target optimizing rate control and more widespread and effective prophylactic anticoagulation.

Introduction

The reported prevalence of atrial fibrillation (AF), the commonest cardiac arrhythmia in clinical practice, is 0.1% in persons aged <55 years and 9.0% in those aged

≥80 years [1]. Being age-related, it is the 'new epidemic' of cardiovascular disease afflicting ageing (Western) societies [2]. When chronic, it is associated with congestive heart failure, valvular, hypertensive and

coronary artery heart disease [3]. After adjusting for these underlying conditions, AF is nevertheless associated with a 1.5–1.9-fold increase in mortality and a doubling of overall morbidity, in both men and women across a wide spectrum of ages [4, 5].

AF's highly variable clinical presentation ranges from absence of symptoms to heart failure and haemodynamic collapse [6]. Multivariate analysis has identified increasing age, heart failure, smoking, diabetes, hypertension, male sex, left ventricular hypertrophy, myocardial infarction, and valvular heart disease as risk factors [7]. Most symptoms (palpitation, lightheadedness/dizziness, dyspnoea, and angina) are attributable to poorly controlled or irregular ventricular rate [8]. AF patients may also endure reduced quality of life (exercise capacity) and serious complications including: systemic embolism, haemodynamic dysfunction and tachycardia-mediated cardiomyopathy [9]. In AF, the attributable risk of stroke increases two- to threefold with each decade; from about 1.5% in persons aged 50–59 years to around 23.5% in those aged 80–89 years [10]. Thus, AF becomes an increasingly major health problem in ageing populations.

If feasible, restoring sinus rhythm by electrical cardioversion and antiarrhythmic drugs was generally favoured; arguably, there was better alleviation of symptoms (including improved exercise tolerance) and the need for anticoagulation was eliminated. However, high-profile, recently published randomized controlled trials (RCTs) comparing outcomes in AF patients assigned to rhythm vs. rate control strategies challenge this assertion [11, 12]. Although editorials and review articles commenting on this issue as well the pharmacological and other means of achieving optimal results have followed [13–18], as yet there has been no meta-analysis of studies comparing the two strategies. Moreover, to consider the influence of rhythm control only in terms of relative risks could well mislead, depending on the frequency with which different desirable or undesirable endpoints are encountered. For a better appreciation of whether or not rhythm control might nevertheless be preferable to rate control, it is necessary to assess its impact in terms of absolute harm or benefits conferred on diverse, clinically relevant parameters. In this context, number needed to treat (NNT) is a function of absolute risk reduction or absolute risk increase, by which it is possible to construe absolute harm or absolute benefit.

We therefore set out to derive: (i) unadjusted relative risk reductions (RRRs) as well as (ii) NNT year⁻¹ individual trials and corresponding comprehensive weighted values for all trials combined, for several clin-

ically relevant outcomes reported in studies comparing rhythm vs. rate control strategies in representative patients with spontaneous AF.

Methods

The PubMed, Medline and Cochrane databases were searched for RCTs having an English abstract containing the key terms: atrial fibrillation, rate control and rhythm control. Only trials primarily comparing rhythm vs. rate control strategies in spontaneously ensuing AF, reporting hard clinical outcomes and recruiting ≥200 patients were selected.

Patient numbers having or not having the following outcomes were recorded: deaths from any cause; hospitalization for any cause; 'non-CNS' bleeding; 'ischaemic' strokes. Rhythm control was assumed to be the active intervention. Based on available published data, unadjusted RRRs and 95% confidence intervals (CIs) for each endpoint were determined for individual trials. Similarly, for each outcome, NNT year⁻¹ values (product of NNT and years of follow-up) and corresponding 95% CIs were derived for individual trials together with a combined NNT year⁻¹ and 95% CIs for all trials (weighted by each trial's sample size and average follow-up duration) as previously described [19, 20]. Microsoft Excel 2000 was utilized for all of these calculations. Any negative value implied harm (higher risk for the adverse event of interest in the rhythm control group). Heterogeneity between individual trials was tested using a software program (Comprehensive Meta Analysis™; Biostat Inc., Englewood, NJ, USA) applied to relative risk ratios.

Reported adverse drug reactions (ADRs) and quality of life scores were also examined.

Results

The selection of studies for this systematic review and meta-analysis is outlined in Figure 1. The five trials identified for inclusion were: Pharmacological Intervention in Atrial Fibrillation (PIAF) [21], Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) [11], Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) [12], Strategies of Treatment of Atrial Fibrillation (STAF) [22], and How To Treat Chronic Atrial Fibrillation (HOT CAFE) [23, 24]. Table 1 details demographic and other information pertinent to these trials. All 5239 patients had 'persistent' or 'recurrent' AF that was variously defined in each trial. In the main, recruitment depended on a need to offer long-term treatment based on clinical judgement. All these trials used intention to treat analyses, but only AFFIRM and RACE mentioned conceal-

Figure 1

Trial flow

ment/censoring of treatment assignment from endpoint assessors.

Table 2 shows RRRs and their 95% CIs for the selected endpoints in each trial. In terms of avoiding hospitalization, all trials favoured rate control ($P < 0.01$); all RRRs being negative and associated 95% CIs did not overlap zero. For all other endpoints, no statistically significant difference between the two treatment strategies was observed. Based on relative risk values, our meta-analysis program yielded statistically significant heterogeneity between relevant trials only with respect to data for hospitalization ($P < 0.001$). For successive meta-analysed outcomes, forest plots showing NNT year⁻¹ and respective 95% CI values for individual trials and all trials combined are illustrated in Figure 2.

Although there was no significant difference between treatment arms for 'ischaemic' stroke presumed thromboembolism (see Figure 2D), irrespective of assignment, most ensued in patients whose warfarin dosage was subtherapeutic or had ceased [11, 12]. Quality of life, scored by the Medical Outcomes Study short-form health survey (SF-36) questionnaires was separately assessed in PIAF and STAF, and both trials recorded similar improvements with both strategies. Most ADRs (attributable to antiarrhythmic agents) manifested in patients assigned to rhythm control. In AFFIRM, Torsade, bradycardia and prolonged QT intervals were each significantly more common in rhythm control patients ($P < 0.001$). Whereas the relative risks for encountering these complications were high (6.0, 9.0 and 7.7, respec-

tively), in absolute terms, the risks were nevertheless low (respective NNT year⁻¹ values being -712, -890 and -264). In RACE, severe ADRs of antiarrhythmic agents included sick sinus syndrome/atrioventricular block, ventricular fibrillation, rapid ventricular rate and heart failure. They occurred in 12 rhythm control patients. Two patients assigned to rate control experienced nonlethal digitalis intoxication. Drug-related side-effects were found in 47% of rate and 64% of rhythm control patients in PIAF; mainly diltiazem-related peripheral oedema in the former and amiodarone-related corneal deposits, photosensitivity and thyroid problems in the latter. Consequential change in therapy ensued in 14% and 25% of those assigned to rate and rhythm control, respectively ($P = 0.036$). In HOT CAFE, four drug-induced arrhythmias were reported in the rhythm control group as opposed to none in rate control patients.

Discussion

Restoration of sinus rhythm in AF patients was purported to confer many benefits, including: symptom relief, improved exercise tolerance and haemodynamic function, avoidance of stroke and the inconvenience and risks of long-term anticoagulation, and the prevention of tachycardia-induced cardiomyopathy [25]. It was also suggested that 'AF begets AF' [26]. However, drugs used to maintain sinus rhythm are often ineffectual and associated with ADRs [27, 28]. Without antiarrhythmic drugs, only 25% of patients are in sinus rhythm at the end of 1 year, as opposed to 50–60% in those who continue taking them [29]. Moreover, restoration of sinus rhythm usually requires electrical or pharmacological cardioversion, or even surgical or catheter ablation, atrial pacing, or internal atrial defibrillation [29]. Such therapy obviously entails high costs and the need for frequent hospitalizations.

A more cost-effective approach could be to control ventricular rate without aiming to attain sinus rhythm by the administration of digoxin, β -blockers or nondihydropyridine calcium channel antagonists (diltiazem or verapamil) [30]. Heart rate is considered controlled when it is 60–80 min⁻¹ at rest and 90–115 min⁻¹ during moderate exercise [14]; there being a linear relationship between resting heart rate and life expectancy [31]. Moreover, the rate control approach did not confer inferior quality of life, according to the findings from PIAF and STAF as well as a subsidiary posthoc study on RACE patients [32]. When pharmacotherapy fails to control ventricular rate, atrioventricular node ablation and permanent pacing can be tried. Regrettably, patients in AF are at increased risk of thromboembolism, includ-

Table 1

Trial characteristics

(Year)	Mean FU, years	Treatment group	No. of subjects	Males, %	Mean age, years (SD)	Drugs/other interventions	Protocol for thromboembolic Px
AFFIRM (2002)	3.5	Rhythm control	2033	62	70 (9)	Electrical cardioversion, amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, dofetilide*	OA encouraged
		Rate control	2027	59	70 (9)	β-blockers, verapamil/diltiazem, digoxin*	OA mandated
RACE (2002)	2.3	Rhythm control	266	64	68 (8)	Electrical cardioversion + sotalol, flecainide, propafenone, amiodarone	OA could be stopped or changed to aspirin
		Rate control	256	63	68 (9)	Digitalis, verapamil/diltiazem, β-blocker*	OA, but aspirin could be substituted if <65 years of age
STAF (2003)	1.6	Rhythm control	100	59	65 (9)	Electrical cardioversion + Class I antiarrhythmic agent, sotalol (no CHD nor LV dysfunction) or other β-blocker and/or amiodarone (CHD or LV dysfunction)	OA as per ACCP guideline [20]
		Rate control	100	68	66 (8)	β-blockers, digitalis, verapamil/diltiazem,* or AV nodal ablation + pacemaker	
PIAF (2000)	1	Rhythm control	127	72	60 (10)	Amiodarone ± electrical cardioversion	100% on OA
HOT CAFE (2003)	1	Rate control	125	74	61 (9)	Diltiazem ± others	100% on OA
		Rhythm control	104	68	60 (8)	Electrical cardioversion + amiodarone	OA as per ACCP guideline [20]
		Rate control	101	62	61 (18)	Verapamil/diltiazem, β-blocker, digoxin*, amiodarone or AV nodal ablation + pacemaker	

*Given singly or in combinations. CHD, coronary heart disease; LV, left ventricular; OA, oral anticoagulation.

Table 2

Relative risk reduction (95% CIs) for all endpoints in individual trials (assuming rhythm control as the active intervention)

	Death	Hospitalization	'Non-CNS' bleeding	'Ischaemic' stroke
AFFIRM	-15 (-34, 2)	-12 (-22, -4)	11 (-19, 33)	-4 (-43, 25)
RACE	4 (-88, 51)*		28 (-74, 70)	
STAF	50 (-70, 85)	-108 (-235, -29)†	-38 (-248, 46)	-400 (-4372, 44)
PIAF	2 (-627, 87)	-185 (-336, -87)		
HOT CAFE	-191 (-2833, 71)	-523 (-1059, -235)	-55 (-386, 50)	‡

*Strictly for CVS death only. †CVS hospitalization. ‡As no patients suffered from ischaemic stroke in rate control group, relative risk reduction (RRR) cannot be determined due to division by zero. AFFIRM and HOT CAFE did not explicitly distinguish what they termed 'ischaemic' strokes from transient ischaemic attacks (TIAs); in STAF ischaemic stroke/TIAs were considered together. These tertiary institutions were presumed to have carried out suitable imaging to exclude cerebral bleeds, which were separately identified in AFFIRM.

Table 3Meta-analysis of treatments for atrial fibrillation by NNT year⁻¹ (assuming rhythm control as the active intervention)

Trials	Mean FU (years)	No. with event No. treated	No. with event No. of controls	NNT year ⁻¹ *	NNT year ⁻¹ 'lower' 95% CI	NNT year ⁻¹ 'upper' 95% CI
(A) Death						
AFFIRM	3.5	356/2033	310/2027	-158	5886	-78
RACE†	2.3	18/266	18/256	870	50	-56
STAF	1.6	4/100	8/100	41	15	-64
PIAF	1.0	2/127	2/125	3969	32	-33
HOT CAFE	1.0	3/104	1/101	-53	54	-18
Combined	—	383/2630	339/2609	-199	1142	-92
(B) Hospitalization						
AFFIRM	3.5	1374/2033	1220/2027	-47	-79	-34
STAF‡	1.6	54/100	26/100	-6	-11	-4
PIAF	1.0	87/127	30/125	-2	-3	-2
HOT CAFE	1.0	75/104	12/101	-2	-2	-1
Combined	—	1592/2364	1288/2353	-35	-48	-27
(C) 'Non-CNS' bleeding						
AFFIRM	3.5	96/2033	107/2027	629	184	-446
RACE	2.3	9/266	12/256	176	49	-111
STAF	1.6	11/100	8/100	-54	32	-15
HOT CAFE	1.0	8/104	5/101	-36	26	-11
Combined	—	124/2503	132/2484	607	187	-489
(D) 'Ischaemic' stroke						
AFFIRM	3.5	80/2033	77/2027	-2567	333	-265
STAF	1.6	5/100	1/100	-41	235	-19
HOT CAFE	1.0	3/104	0/101	-35	301	-16
Combined	—	88/2237	78/2228	-976	430	-229

*Positive values refer to NNT(benefit) year⁻¹ and negative values to NNT(harm) year⁻¹. †Strictly CVS death only. ‡CVS hospitalization.

ing stroke. The latter risk is particularly significant in patients having hypertension, coronary artery disease, left ventricular dysfunction, prior thromboembolism and those aged >65 years, for all of whom life-long anticoagulation is indicated [32]. Rate control is also associated with specific dysfunctions (atrial remodelling and loss of atrial contraction) [33].

NNT refers to the number (of persons) that need to receive a given treatment over a specified period of time, so as to prevent one of them from experiencing the event of interest (e.g. stroke). Compared with RRR, NNT (the reciprocal of absolute risk reduction) conveys a much better idea of an intervention's absolute cost-effectiveness by taking account of: (i) event-related reductions in longevity and quality of life, and (ii) consequential direct and less tangible treatment costs, both of which are presumed to be averted. NNT also facilitates appreciation of the numbers of subjects exposed to possible adverse effects and inconvenience of the necessarily

prescribed long-term medication, just to benefit one individual. Generally, the benefits conferred by long-term interventions are assumed to be evenly distributed over time and therefore NNT is considered to be inversely related to treatment duration. Under the circumstances, for any given endpoint it is not sufficient to note prevailing NNT values without considering treatment duration. All NNTs and their respective 95% CIs were therefore adjusted and expressed as NNT year⁻¹ values. With respect to derivation of an NNT for the prevention of an adverse disease outcome, a value of infinity is equivalent to no effect, whereas smaller and smaller values indicate greater and greater impact; benefit if positive and harm if negative. This explains the format of the horizontal axis scale [34] we opted to use in our meta-analyses of NNT year⁻¹ values.

The five RCTs selected for the present review/meta-analysis enrolled a relatively homogeneous group of subjects representative of the majority of patients with

AF: elderly men and women with persistent or intermittent symptomatic AF and risk of stroke [1]. Clinically, minor degrees of heterogeneity were nevertheless evident. Thus, the drugs utilized for rate control or to maintain sinus rhythm varied between and within trials and long-term oral anticoagulation for patients assigned to both groups was only mandatory in PIAF. In RACE, only cardiovascular mortality was detailed and assumed by us to represent total mortality. Similarly, STAF reported only hospitalizations for cardiovascular disorders, which were presumed to represent all admissions. From a statistical perspective, however, for all endpoints except hospitalization there was no heterogeneity between trials, in as much as the respective 95% CIs for NNT year⁻¹ values always overlapped. Similarly, according to the statistical test in our meta-analysis software, based on relative risk, heterogeneity was evident only for hospitalization. This may be attributable to dif-

ferences in drug treatment regimes as well as intercontinental divergence (North America vs. Europe) in management policies.

AFFIRM, the only trial sufficiently powered to assess death as a separate endpoint, did not yield a statistically significant increase in mortality, but there was a trend. Not surprisingly, a trend in favour of rate control was also observed for the combined NNT year⁻¹ value (-199).

All four trials reporting hospitalizations yielded statistically significant differences in favour of rate control, the combined NNT year⁻¹ being -35. Thus, for every 35 patients assigned to rhythm control, one additional person per year was liable to hospitalization (mostly for electrical cardioversion or ADRs). This also has important cost implications, which have been amply confirmed by subsidiary economic evaluations on AFFIRM and RACE trial patients [35, 36]. Even after applying

Figure 2

Meta-analysis of treatments for atrial fibrillation by NNT year⁻¹ (assuming rhythm control as the active intervention)

sensitivity analyses over a wide range of assumptions, the latter studies consistently substantiated the greater cost-effectiveness of rate control in comparison with rhythm control and therefore attested to the robustness of their conclusions.

The importance of maintaining adequate levels of adjusted-dose oral anticoagulation even after restoration of sinus rhythm is compelling [13, 14, 16] and appears more efficacious than taking aspirin [16, 37]. Clearly, cessation of anticoagulation, a main reason for restoring sinus rhythm, cannot be sustained, but whether asymptomatic AF recurrences result in such thromboembolism still needs to be established [38]. Although there was no significant difference between rate and rhythm control groups in terms of 'non-CNS' bleeding (Figure 2C), there was a lower rate of this complication in the latter patients (consistent with the smaller proportion receiving anticoagulants), the combined NNT year⁻¹ for prevention of such bleeding being 607.

Restoration of sinus rhythm by so-called class IA, IC and III antiarrhythmics might offer a theoretical advantage by preventing remodelling, but gives rise to serious or even lethal arrhythmias. Such ADRs may partly explain the higher frequency of hospitalizations and medication crossover rates, particularly in patients with left ventricular dysfunction, congestive heart failure or ischaemic heart disease [39].

Since the present meta-analysis was not based on individual patient data, the scope for exploratory analyses of outcomes in relevant subgroups was inevitably limited. A further caveat is that findings from these studies are not applicable to younger persons or patients having atrial fibrillation with significant symptoms [13, 40]. However, in the absence of any other clinical outcome studies specifically targeted at the latter groups, what strategy to offer such patients remains unclear.

In conclusion, our systematic review/meta-analysis demonstrated no advantage in establishing and maintaining sinus rhythm with currently available therapies and concurs with other reviews [13, 15, 40, 41]. Mortality and ischaemic stroke incidence trends, and the clinically and statistically highly significant differences in hospital admission and ADR rates all favour rate control. Irrespective of treatment assignment, the need for adequate anticoagulation appears paramount. Thus, currently deployed strategies directed at rhythm control in representative patients with AF impose an unwarranted clinical and financial burden. If symptoms associated with rate control are not an issue, the focus of patient management should be redirected to (i) optimizing the means of rate control, and (ii) more universal and better long-term thromboembolic prophylaxis.

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