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What can rhythm control therapy contribute to prognosis in atrial fibrillation?

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ABSTRACT

Atrial fibrillation (AF) is a global healthcare problem of growing prevalence and major significance. The consequences of AF include an increased rate of death, stroke and heart failure. Theoretically, a therapeutic strategy aiming at restoration and maintenance of sinus rhythm should offset the prognosis impairment associated with AF. However, these expectations were disproven in large randomised controlled trials comparing conventional antiarrhythmic drugs for rhythm control with conventional rate control. These apparently contradictory findings suggest that rhythm control strategies require better therapeutic instruments. These improvements may involve drugs and/or interventions with optimised risk–benefit profile and which also appreciate the specific atrial pathology and the patient's comorbidities. This article addresses important aspects of rhythm control strategies, which may have the potential of a beneficial contribution to the prognosis of AF patients.

INTRODUCTION

Atrial fibrillation (AF)—the most common sustained arrhythmia encountered in clinical practice—is characterised by chaotic atrial activation resulting in loss of distinct p waves on the surface ECG as well as an irregular ventricular response. Pathophysiological mechanisms contributing to the initiation and perpetuation of AF are multifactorial and interindividually variable. Functional and structural changes in the atria (remodelling) can promote AF by variety of processes involving ion channel remodelling, inflammation, fibrosis, loss of cell–cell contacts and apoptosis. Clinical consequences include the loss of atrioventricular synchrony, rapid and irregular ventricular rates that result in negative consequences on cardiac perfusion and performance, as well as increased myocardial oxygen demands and an increased risk of cardiomyopathy. The main adverse events of AF include thromboembolism (strokes in particular), congestive heart failure (CHF) and death. AF has been shown an independent predictor of mortality with a gender-specifically increased risk of death.[1] Although AF can occur as so-called 'lone AF' or inherited, it is most often associated with other cardiovascular risk factors and comorbidities, particularly hypertension, valvular heart disease or cardiomyopathy. Until now, it is not entirely clear, whether AF is a causative risk factor or simply a marker of risk.

Contemporary treatment strategies focus on symptoms as well as the risk of heart failure and thromboembolism. Antithrombotic therapy is so far the only treatment component, which has been shown to reduce AF-related deaths. Rhythm control through sinus rhythm (SR) restoration and maintenance is usually attempted in patients, in whom ventricular rate control is clinically insufficient. Provided that AF is causally related to increased mortality, resumption and maintenance of SR is expected to alleviate these risks and counterbalance impaired prognosis. However, a variety of randomised controlled trials have failed to demonstrate a mortality benefit of a rhythm and rate control strategy with antiarrhythmic drugs (AADs) over conventional rate control alone. These apparently contradictory findings suggest that the prognostic effect of a rhythm control strategy is more complex.

In order to address the contribution of rhythm control therapy to prognosis, this article elaborates important conclusions as well as shortcomings of published randomised controlled trials, and discusses the clinical potential of modern targeted and individualised treatment concepts and the potential clinical role of biomarkers.

RATE VERSUS RHYTHM CONTROL

The two treatment concepts of rate versus rate and rhythm control (abbreviated rate vs rhythm control in the following) have been compared with mortality endpoints in several controlled randomised multi-centre clinical trials (see online supplement 1 for detailed comparison).[2] None of these studies could demonstrate a mortality benefit of one treatment strategy over the other. Several aspects deserve further consideration in order to draw valid conclusions. In fact, relevant aspects directly or indirectly derived from these studies highlight the potential prognostic role of a rhythm control strategy:

A. Efficacy–risk profile of AADs

In all relevant rate versus rate and rhythm control trials, rhythm control strategies were exclusively based on AADs. These agents have generally demonstrated a limited efficacy in restoring stable SR, ranging from 26% to 63%.[3 4] Moreover, almost all AADs have a certain risk of relevant cardioinhibitory and proarrhythmic effects, especially in patients with structural heart disease. Due to their risk of proarrhythmia, class-I AADs are reserved for patients free from cardiac diseases. For patients with structural heart disease, amiodarone is the most effective and safest choice. Thus, amiodarone is predominantly used in clinical trials with AADs. However, even amiodarone is known to increase mortality in patients with CHF, and exhibits substantial extracardiac adverse effects such as pulmonary and hepatic toxicity and thyroid dysfunction—leading to high rates of drug discontinuation in the

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long term. These proarrhythmic effects and non-cardiac toxicities, combined with limited clinical efficacy and high discontinuation rate most likely counterbalanced beneficial prognostic effects of SR maintenance.[5]

B. Rhythm control and age

In the Atrial Fibrillation Follow-up Investigation of Rhythm Management trial (AFFIRM) patients of advanced age (70–80 years, matched for 45 baseline characteristics), rate control therapy was associated with a 23% lower all-cause mortality, which was mainly driven by a 38% lower non-cardiovascular mortality.[6] These observations are in line with the results of an exploratory analysis in patients younger than 65 years pooled from 10 comparative studies, demonstrating that a rhythm control strategy was associated with a lower all-cause mortality compared with rate control.[2] Thus, harmful effects of a rhythm control strategy seem to correlate with age. It should be noted that previous clinical trials focused on elderly patients with risk factors for stroke and death, whereas younger patients with lone paroxysmal AF were under-represented.

C. Role of heart failure in AF

AF and structural heart disease (especially CHF) share complex interrelations. Due to similar risk factors, both entities often coexist and promote each other. The prognosis of each condition alone is often further worsened on the emergence of the other. New-onset AF occurring in patients with pre-existing CHF may indicate acute disease severity, rendering restoration of stable SR more unlikely to prevent worsening CHF or death. On the other hand, the existence of AF-related cardiomyopathies has been demonstrated, which may be cured by successful SR maintenance with potential benefits on prognosis. In the AF–CHF trial, no prognostic benefit of rhythm control over rate control was found in patients with CHF history for at least 6 months.[7] This may, at least in part, be explained by the observation in a subanalysis of Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation study (RACE), demonstrating that the underlying heart disease in combination with inefficacious and adverse drugs exerts such a negative effect on morbidity and mortality, which long-term normal SR cannot counterbalance.[8]

D. Anticoagulation in rhythm-controlled patients

Thromboembolic events in the RACE rhythm control arm were more common in patients who had stopped anticoagulation or had an insufficient international normalised ratio (INR). Similarly, most patients who experienced strokes in the AFFIRM study were not on warfarin or had a subtherapeutic INR at the time of stroke.[4] Obviously, the premature cessation of oral anticoagulation in one-third of rhythm-controlled AFFIRM patients made them vulnerable to thromboembolic consequence. The decision to stop oral anticoagulation remains challenging, because a large proportion of AF recurrences is clinically silent, both after pharmacological or interventional rhythm control and continuous and reliable ECG monitoring is not realistically available for every patient.

E. Length of follow-up

The time frame required for AF to exhibit negative consequences on patient prognosis is unknown. Thus, the follow-up duration used in the above-mentioned comparative studies (3–5 years) may have been too short to prove a beneficial effect of rhythm over rate control. In fact, an analysis of the Canadian population-based administrative databases seems to support this hypothesis. Among 26,130 patients >66 years of age with a new AF-related prescription, after adjusting for covariates, mortality in patients treated with rhythm control was higher compared with rate-controlled patients in the first 6 months following treatment initiation. However, the mortality was similar in the two groups until year 4, but decreased steadily in the rhythm control group after year 5.[9] These results indicate that longer follow-up periods may be necessary to demonstrate the anticipated benefits of rhythm control on the prognosis.

NOVEL OPTIONS FOR RHYTHM CONTROL

Antiarrhythmic drugs

In order to overcome the current limitations of contemporarily used AADs in terms of efficacy and safety (ventricular proarrhythmia in particular), investigational efforts focus on novel targets underlying molecular AF mechanisms. These targets include atrial-selective ion currents (eg, via ultrarapid delayed rectifier potassium channels or acetylcholine-dependent potassium channels), intracellular calcium handling (eg, via ryanodine receptors), non-ion channels influencing electrical and structural remodelling (eg, via microRNAs), gap junctions (eg, via connexins) and others.[10] Even drugs aiming at the prevention of fibrotic remodelling (upstream therapy) may be considered as rhythm controlling agents in a broader sense. These drugs target either the angiotensin system, transforming growth factor-β1 signalling, pathological oxidative stress or inflammation.[10] Most of these compounds are still under preclinical investigation. In the recent years, only two AADs have been approved for clinical use, both with moderate success. Dronedarone, an amiodarone derivative with an improved safety profile reduced cardiovascular mortality, strokes and hospitalisations in (predominantly paroxysmal) AF patients in the placebo-controlled 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 (ATHENA) trial.[11] However, the drug was less effective than amiodarone in terms of SR maintenance, and an excess of adverse cardiovascular outcomes were observed in persistent AF patients and CHF patients. The combination of dronedarone with other agents could possibly augment efficacy and safety. Thus, combined administration of dronedarone with ranolazine has been reported to result in a potent protection not only against AF but also against vulnerability to ventricular arrhythmias.[12] However, these results need to be confirmed in clinical practice. Vernakalant blocks repolarising potassium currents predominantly working in atrial cells (IK_{ur} and I_{to}) as well as voltage-dependent and frequency-dependent sodium channels in the atria and ventricles. In a series of clinical studies (resulting in approval in Europe), intravenous administration of the drug demonstrated rapid conversion of recent-onset AF to SR in approximately half of the patients. Hypotension and bradycardia belong to the most frequent side effects, but ventricular proarrhythmia was not observed. Although the drug is in general considered safe, severe adverse events with fatal outcome after vernakalant administration have been reported.[13] Oral vernakalant, currently under evaluation for the maintenance of SR, seems to be more effective than placebo, but not in the range of amiodarone.

Catheter ablation

Pulmonary vein isolation (PVI) has become the recommended cornerstone of any catheter ablation (CA) approach, since the interaction of triggers (primarily from firing pulmonary veins) and substrate had been established. Although a clear relationship between clinical AF phenotype and the underlying pathophysiology has not yet been proven, it is thought that triggers play a more important role in paroxysmal AF, whereas the vulnerable atrial substrate is more relevant in chronic forms of AF, where

PVI alone seems less effective. Additional substrate modification seems to be necessary in these patients, which involves atrial defragmentation and/or empirical linear lesion to prevent atrial macroreentries.

A. Comparison with AADs

Several randomised studies compared CA versus AADs for rhythm control in AF patients (see online supplement 2 for detailed comparison).[14–16] These trials consistently demonstrated greater efficacy of CA over AADs in terms of SR maintenance. However, in the most recent studies including AAD-naïve patients the difference in rhythm outcome is less pronounced.[15 16] A summary of available data on the effect of CA on different outcomes but also potential shortcomings and pitfalls is provided in table 1.

B. Effects on prognosis

While the drugs versus ablation trials are very much consistent and underline a general superiority of CA over AADs in terms of SR maintenance and major side effects, available data on the prognostic impact of CA are limited. Bunch and colleagues found that a total of 4212 consecutive patients from the large ongoing prospective Intermountain AF Study following CA of AF did not only have a lower risk of death and stroke after 3 years compared with 16 848 age-matched/gender-matched AF without ablation, but demonstrated similar rates of death and stroke as 16 848 age-matched/gender-matched controls without AF.[17] Similarly, Hunter and coworkers[18] demonstrated that death rates during 3 years of follow-up of >1000 patients from an international multi-centre AF Ablation Registry were significantly lower compared with a control group of medically treated patients in the Euro Heart Survey, and similar to a hypothetical patient cohort without AF, age matched and gender matched to the general population. A significant prognostic impact by CA can be expected in AF patients with impaired LV systolic function. In these patients, CA seems to be equally effective as in patients without heart failure, and LV function consistently improves in a significant proportion of patients.[19]

Ongoing randomised controlled trials will provide evidence on the prognostic effects of modern rhythm control treatment concepts. The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation trial (CABANA) trial will provide important information whether CA is superior to current state-of-the-art medical therapy comprising rate or rhythm control drugs in patients with AF and increased risk. The primary endpoint is a composite of total mortality, disabling stroke, serious bleeding or cardiac arrest. Secondary endpoints also relate to quality of life and healthcare resource utilisation. Unlike previous drugs-versus-ablation studies, this trial will compare a palliative pharmacologic AF strategy with a potentially curative interventional strategy. In contrast to CABANA, Early Treatment of Atrial Fibrillation for Stroke Prevention trial (EAST) tests the impact of a structured, early application of rhythm control therapy encompassing CA and/or AADs on hard endpoints compared with usual care alone. The study also examines hard combined mortality endpoints and will add further evidence to the observation that beneficial prognostic effects of rhythm control are most likely to be seen in younger patients with early stages of the disease.[20]

C. Combined ablative and pharmacological approach

Naturally, CA and the administration of AADs are not mutually exclusive. Thus, in clinical practice, AADs are often given after ablation in order to improve health outcomes. Reports on the effect of this approach are controversial with some studies indicating a beneficial effect of antiarrhythmics on secondary endpoints such as reduction of hospitalisations,[21] but a clinically considerable effect on recurrences has not been confirmed.[21 22]

D. Novel strategies and technological improvements

Numerous technological advances aim at improving the risk–benefit profile of the procedure as well as reducing its duration, complexity and x-ray requirement.[10] Relevant increase of efficacy rate is most likely expected from novel ablation strategies. New individualised ablation approaches target substrate changes, which vary widely even among patients with similar patterns of AF and may have a significant effect on the ablation outcome. For example, novel therapeutical concepts refer to structural changes like tissue scarring and atrial fibrosis subsequent to atrial remodelling processes. These structural changes

Table 1 Summary of outcomes and shortcomings of clinical studies comparing catheter ablation (CA) or antiarrhythmic drugs (AADs) for rhythm control of atrial fibrillation (AF)

Outcomes	Effect of ablation
Mortality	Most important outcome but insufficient available evidence with no solid data on ablation effect up to now. Limited evidence from non-randomised studies that after ablation the rate of death may be similar with non-AF patients. Currently under investigation in large, randomised trials (EAST, CABANA)
Stroke, need for anticoagulation	Very important outcome. Observational studies indicate a reduction of stroke risk after ablation, especially in patients who maintain sinus rhythm. The possibility of anticoagulation cessation after successful ablation needs further investigation
Arrhythmia recurrence	Solid data from multiple randomised trials on significant reduction of recurrences following ablation compared with AADs
Progression of arrhythmia	Not sufficiently studied. Some evidence for low progression rates to persistent or permanent AF, especially when ablation is performed in the paroxysmal phase. The clinical significance needs further elucidation
Possible shortcomings	
Patient selection	Patient selection in terms of AF type, underlying heart disease and comorbidities differs between studies and needs appreciation before drawing conclusion on individual patient; in most studies, patients already failed AAD attempts, possibly implying a negative preselection
Methods	CA alone or as an adjunct to AAD therapy; high and unequally distributed crossover rates
Ablation procedure	Procedural strategies, endpoints, tools and techniques are not standardised; decision for extended substrate modification often based on rather soft clinical variables like AF type/duration not necessarily reflecting the electrophysiological pathology; variable operator experience; all these factors complicate intrastudy/interstudy comparisons and directly affect procedure efficacy and risk
Study centres	Ablation outcome from very experienced high-volume centres may not be translated straight to the majority of interventional EP laboratories
Method of follow-up	Wide variation of endpoint definition and quality of follow-up in clinical studies directly affecting procedural success: with more intense follow-up, more (asymptomatic) recurrences are detected
Stage of diagnosis	Evidence of a more pronounced beneficial effect when ablation is performed at an early stage. Questioned by the wide variability of underlying substrate changes, as evidenced by novel imaging techniques, among patients at the same arrhythmia stage

EP, electrophysiology.

may be detected by imaging techniques like late gadolinium enhancement in cardiac MRI and/or electroanatomic voltage mapping. The degree of atrial fibrosis seems to correlate with rhythm outcome after standard CA.[23] An individualised CA approach directly targeting low voltage areas seems to have the potential to improve rhythm outcome.[24] Another example refers to focal impulses and rotors, which have been suggested as important factors for AF perpetuation. Based on this concept, a technology for modulation of stable focal impulses and rotors modulation (FIRM) using basket catheters for high-density simultaneous mapping in the atria has been developed. Direct or coincidental FIRM on top of conventional PVI was able to improve mid-term and long-term AF ablation outcomes.[25] Apart from the reduction in recurrences, another important but not well-studied outcome is progression of AF. Ablation therapy has been reported to result in low progression rates to persistent or permanent AF, especially when performed in the paroxysmal phase.[26] However, the clinical significance of these findings needs further elucidation.

ROLE OF BIOMARKERS

As mentioned earlier, mechanisms contributing to the initiation and perpetuation of AF show a high diversity and interindividual variability involving ion channel remodelling, inflammation, fibrosis, loss of cell–cell contacts and apoptosis. Biological markers in the sense of mapping and imaging tools (as mentioned above) as well as biomarkers in blood or urine may serve as new diagnostic tools to identify patients in early stages of remodelling processes enabling effective preventive or curative therapy (figure 1).[27] Moreover, biomarkers indicating genetic predisposition as well as AF-related pathologic conditions like inflammation, hypercoagulable state and endothelial dysfunction may also be used to identify AF patients at very low or very high risk of stroke and thromboembolism. Addition of biomarkers to clinical risk scores has already been shown to increase precision of risk prediction and may be helpful to further individualise treatment strategy and intensity.[28 29]

SUMMARY AND CONCLUSIONS

SR maintenance makes intuitive sense considering the impaired prognosis associated with AF, but numerous comparative studies did not show a prognostic benefit of rhythm over rate control strategy. The question arises whether AF may rather represent a risk marker than a curable causal factor. Several conclusions can be drawn from the available literature. First of all, the AADs used in the rhythm control studies are far from being perfect in terms of their efficacy–risk profile. Safer and more targeted agents as well as more individualised interventional strategies based on the underlying atrial substrate will more likely contribute to the anticipated beneficial effects of a treatment concept aiming at rhythm control. Dronedarone, which is the only new oral AAD released for years, has demonstrated prognostic benefit in paroxysmal AF patients selectively. However, its efficacy in terms of SR maintenance is modest, which may be improved by combined use with other drugs. Intravenous vernakalant—affecting predominantly atrial ion channels—showed some cardioversion potential for recent-onset AF, but safety issues are not completely cleared. Oral vernakalant for SR maintenance is still under clinical evaluation. Specific pharmacological interventions targeting pathological processes in the atrium selectively represent promising tools because of the absent risk of ventricular proarrhythmia, but most of these drugs are still under preclinical investigation. As an interventional alternative for rhythm control, CA has already been proven more effective and safer than pharmacologic rhythm control for certain patient subsets, including patients with depressed LV function. Ongoing technological and strategical refinements are expected to further increase CA efficacy. Certainly, CA carries a certain periprocedural risk, especially in elderly patients, which may cumulate when several sessions are necessary to achieve long-term success. However, it offers the

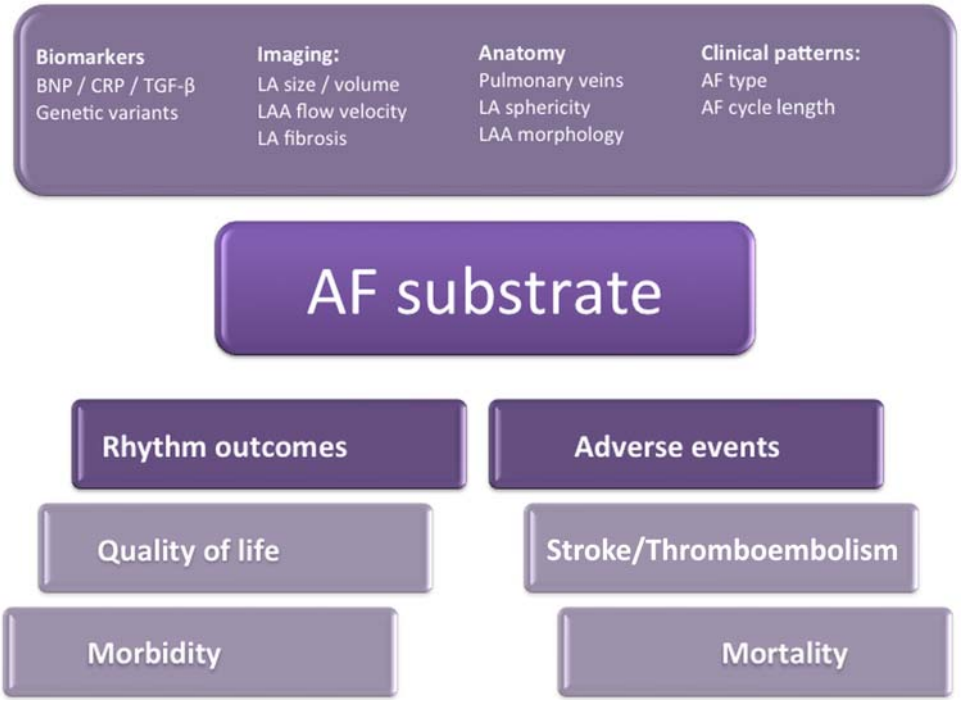

Figure 1 Diagram illustrating factors associated with atrial fibrillation (AF) substrate as well as clinical consequences of the disease condition. BNP, brain natriuretic peptide; CRP, C reactive protein; LA, left atrium; LAA, left atrial appendage; TGF-β, transforming growth factor-β.

chance of cure at least in certain patient subsets, whereas AADs require continuous intake exposing the patient to the potentially life-threatening toxicities. This may be one reason why prognostic benefits of interventional over pharmacological rhythm control will be more obvious in longer follow-up periods. The question whether contemporary rhythm control treatment strategies, including ablative interventions, will actually lead to reductions in stroke and death will ultimately be demonstrated in CABANA and EAST. The issue of anticoagulation surrounding and following rhythm control will also have a relevant impact on prognosis. So far, it is still open and has not yet been studied within the environment of new oral anticoagulants. At present, anticoagulation is recommended according to the individual thromboembolic risk scores irrespective of the clinical success of rhythm control. New diagnostic modalities focusing on biomarkers, including genetics, blood markers and imaging modalities, gain increasing attention. Assessment of certain phenotypical as well as genotypical profiles may allow detection of early stages of structural remodelling enabling timely and individualised therapy. Risk assessment by scores, including new biomarkers, may help to further categorisation of patients according to their individual rhythm outcome and cardiovascular risk.

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