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**SUPPLEMENT PAPER**

# The RACE to the EAST. In pursuit of rhythm control therapy for atrial fibrillation—a dedication to Harry Crijns

**Bruno Reissmann[1]*, Günter Breithardt[2], A. John Camm[3], Isabelle C. Van Gelder[4], Andreas Metzner[1], and Paulus Kirchhof[1,5,6]**

[1]Department of Cardiology, University Heart Center Hamburg, Hamburg, Germany; [2]Department of Cardiology II (Electrophysiology), University Hospital Münster, Münster, Germany; [3]Cardiology Clinical Academic Group Molecular & Clinical Sciences Institute, St George's University of London, London, UK; [4]Department of Cardiology, Thoraxcenter, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [5]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK; and [6]German Center for Cardiovascular Research, Partner Site Hamburg/Kiel/Lübeck, Germany

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**Abstract**

The RACE trial was one of the first landmark trials to establish whether restoring and maintaining sinus rhythm could reduce morbidity and mortality in patients with atrial fibrillation (AF). Its neutral outcome shaped clinical decision-making for almost 20 years. However, there were two important treatment-related factors associated with mortality of rhythm control therapy at that time: One was safety of antiarrhythmic drug therapy, and the other one withdrawal of anticoagulation after restoration of sinus rhythm. Both concerns have been overcome, and, moreover, important knowledge considering the importance of time for the treatment of AF has been gained. These insights led to the concept of the EAST-AFNET 4 trial, and after more than two decades in the pursuit of ongoing therapeutic improvement, early rhythm control therapy has demonstrated to reduce a composite of cardiovascular death, stroke, and hospitalization for worsening of HF or acute coronary syndrome, by 21% (first primary outcome, absolute reduction 1.1 per 100 patient-years). For this entire period, Harry Crijns characterized the treatment of AF patients, and contributed decisively to realizing the benefit of rhythm control therapy. It is almost easier to list the clinical trials without Harry's involvement than to list those which he co-designed and led.

**Keywords** EAST-AFNET 4 • Harry Crijns • Rate control therapy • Rhythm control therapy

Atrial fibrillation (AF) is the most common arrhythmia and a major cause of stroke, heart failure (HF), cardiovascular morbidity, and sudden death.[1] An enhanced understanding of the pathophysiology and the mechanisms causing AF and the improved identification of patients being at high risk for stroke and death helped considerably to assure proper and individualized treatment. Screening for AF in patients being at risk is continuously evolving, in particular, the raised awareness among patients with silent AF, stimulated demand for systematic screening programs. Oral anticoagulation (OAC) therapy constitutes the most important prognostic benefit in AF patients at risk of stroke.[1] Non-vitamin K antagonist oral anticoagulants (NOACs) are a significant progress with half the risk of intracranial bleeding and reduced mortality by ~10% compared with vitamin K antagonist.[2] Management of AF further involves optimal therapy of comorbidities and cardiovascular risk factors. In patients with AF and HF, advanced HF therapy is crucial and supports maintenance of sinus rhythm (SR) independently.[3] However, despite this considerable progress in stroke prevention and optimized therapy of underlying conditions, stroke, cardiovascular death, and unplanned hospitalizations for HF or acute coronary syndrome occur at a high rate (ca. 5%/year).[4,5] The concept that restoring and maintaining SR could help to reduce this remaining morbidity and mortality has been around for a long time.

*Corresponding author. Tel: +49 (0)40 7410-58320. *E-mail address*: b-reissmann@t-online.de

Seven landmark trials directly compared rhythm vs. rate control in a randomized fashion, and their results, published ~20 years ago, shaped the use of rhythm control therapy in patients with atrial fibrillation until 2020.[1] All studies were driven by the question of the prognostic impact of maintaining stable SR in AF patients as compared with pure rate control. The RAte Control vs. Electrical conversion (RACE) trial included 522 patients with persistent AF who were randomly assigned for rate control (pursued by rate-slowing medication) or rhythm control (pursued by serial cardioversions and antiarrhythmic drugs).[6] After a follow-up of >2 years, rate control was non-inferior to rhythm control for the prevention of death and reduction of morbidity. Importantly, the risk of thromboembolic events remained high, even if SR was maintained. Interestingly, substudies of the RACE trial indicated that restoration and maintenance of SR was associated with smaller atrial size, potentially improved atrial function, and better quality of life.[7,8] In accordance with the main results of the RACE trial, the Strategies of Treatment of Atrial Fibrillation (STAF) trial, the How to Treat Chronic Atrial Fibrillation (HOT-CAFE) trial, and the Atrial Fibrillation Follow-up of Rhythm Management (AFFIRM) trial did not show a significant difference of both treatment strategies considering the occurrence of the primary endpoint mainly defined as a composite of death and thromboembolic complications.[6,9–11] With a total of 4060 randomized patients, the AFFIRM trial was the largest of these studies, and although the results of the primary endpoint were equivalent for both treatment arms,[9] a *post hoc* analysis suggested an improved survival in patients with successful maintenance of SR.[10] The Pharmacological Intervention in Atrial Fibrillation (PIAF) trial did not demonstrate improvement of AF-related symptoms by rhythm control therapy by use of amiodarone, but exercise capacity was significantly better with rhythm control.[11] Later, the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial investigated the impact of rate control vs. rhythm control using amiodarone in AF patients with HF and reduced ejection fraction.[12] The concept of the study was to determine whether restoration and maintenance of SR reduces mortality in this patient cohort. Once again, the rhythm control therapy failed to improve outcomes and, moreover, rate control eliminated the need for repeated cardioversion and reduced rates of hospitalization. One notable exception was the positive outcomes of the Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) trial in favour of rhythm control for paroxysmal AF.[13]

The predominant neutral primary outcomes of these studies triggered much rethinking, having regard also to the contradictory results of two subsequent population-based observational studies indicating a beneficial performance of rhythm control.[14,15] One concern was the safety of rhythm control therapy using antiarrhythmic drugs: All antiarrhythmic drugs available for rhythm control therapy at that time were initially developed for the treatment of ventricular arrhythmias, and their efficacy and safety, including effective doses for AF, was only later tested in patients with AF.[16,17] The safety of antiarrhythmic drug therapy was partially addressed in the AF-CHF trial, where only one agent that is considered safe in patients with AF and HF, amiodarone, was used in patients with AF and HF.[12,17] Another important aspect was the practice to discontinue OAC after apparently successful restoration of SR in patients with AF and at high stroke risk, which was the accepted practice at the time, but now known to increase the risk of stroke compared with continued OAC.[18] Use of antiarrhythmic drugs and withdrawal of anticoagulation (except for the PIAF trial) were the two treatment-related factors associated with mortality in these early studies.[18]

Other ideas were tested to improve the safety of antiarrhythmic drug therapy, e.g. episodic therapy with antiarrhythmic drugs as pill-in-the-pocket[19] or short-term therapy.[20,21] While these short-term therapy concepts have the potential to increase the safety of antiarrhythmic drug therapy, the community also learned to use these substances safely as illustrated by the low incidence of pro-arrhythmia in more recent clinical trials.[22,23] The ATHENA trial, although it needs to be viewed in conjunction with the PALLAS and ANDROMEDA studies showing harm when dronedarone was used in patients with permanent, accepted AF,[24,25] demonstrated that treatment with antiarrhythmic drugs (dronedarone) could improve a composite outcome of cardiovascular hospitalization or death, as well as stroke and first occurrence of an acute coronary syndrome in an exploratory subanalysis, in patients with AF.[26,27] But the limited efficacy in maintaining SR remained a limitation of antiarrhythmic drug therapy for patients with AF, especially in patients with recurrent AF on an antiarrhythmic drug. The ion-blocking antiarrhythmic effects were too similar between agents to offer real choice.

The availability of AF ablation,[28,29] which became a routine and reasonably safe procedure ~10 years after the seminal description of AF triggers in the pulmonary veins,[30] improved this situation by providing an additional powerful[22,23] and synergistic[31,32] tool for effective rhythm control therapy in patients with AF. In MANTRA-PAF (Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation), the first study comparing AF ablation with antiarrhythmic drugs in patients without prior rhythm control therapy, safety was comparable and there was only a slightly better effectiveness of AF ablation.[22] Multiple other studies, usually enrolling patients with established and often failed antiarrhythmic drug therapy, demonstrated that AF ablation maintains SR better than antiarrhythmic drug therapy.[28,29,33–35] Therefore, it was hypothesized that catheter ablation might also have beneficial impact on prognostic endpoints such as mortality but also on reduction of stroke risk. As one of the first the Swedish ablation registry demonstrated a significantly reduced incidence of ischaemic stroke as well as mortality in 2496 patients after catheter ablation of AF as compared with the same number of patients without catheter ablation.[36]. In the Ablation vs. Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device (ATAAC) study, patients with AF and HF had a lower rate of AF recurrence after catheter ablation as compared with amiodarone treatment.[37] Although not being adequately powered, the study suggested a lower mortality in patients receiving catheter ablation. Another study enrolling patients with AF and HF with reduced ejection fraction was the Catheter Ablation for Atrial Fibrillation with Heart Failure (CASTLE-AF) study.[38] The study randomized patients to catheter ablation or antiarrhythmic medication. First, it underlined once again the supremacy of ablation over medication concerning maintenance of SR. But it also found a significant benefit in the composite Endpoint of death from any cause or hospitalization for worsening HF in the ablation group. Based on those hypothesis-generating pilot data, results of the Effect of Catheter Ablation vs. Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation (CABANA) study, with more than 2200 patients

**Table 1** Excerpt from major studies of rate and rhythm control therapy for the treatment of atrial fibrillation

| Study (year of publication) | Patients | Treatment | Endpoints | Outcomes |
|---|---|---|---|---|
| RACE (2002)[6] | Persistent AF with previous electrical cardioversion ($n = 522$) | Rate control: β-blockers, calcium antagonist, digoxin (either alone or in combination)<br>Rhythm control: electrical cardioversion followed by AADs (amiodarone, class IC agents, or sotalol)<br>OAC could be stopped in rhythm control group with presence of SR at 1 month after cardioversion | Composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding,<br>the need for implantation of a pacemaker, or severe adverse effects of AADs | Non-inferiority of rate vs. rhythm control ($P = 0.11$)<br>Thromboembolic complications and pacemaker implantation were more likely in rhythm control group |
| AFFIRM (2002)[9] | Paroxysmal and persistent AF ($n = 4060$; ca. 1/3 were enrolled after their first episode of AF) | Rate control: β-blockers, calcium antagonist, digoxin (either alone or in combination)<br>Rhythm control: electrical cardioversion as necessary. AAD therapy (amiodarone, class IC agents, sotalol, and combinations of these drugs) with amiodarone and sotalol being by far the most commonly used drugs<br>OAC could be stopped in rhythm control group with presence of SR for at least 4 weeks | Primary endpoint was overall mortality. Secondary endpoint was a composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest | More deaths when aiming at rhythm control vs. rate control without being statistically significant ($P = 0.08$)<br>No difference considering the secondary endpoint ($P = 0.33$)<br>Significantly higher rate of crossover from rhythm to rate control (rate to rhythm control: 14% vs. rhythm to rate control: 38%; $P < 0.001$)<br>In both arms, most strokes occurred after discontinuation of warfarin or when the INR was subtherapeutic |
| AF-CHF (2008)[12] | Paroxysmal and persistent AF with ICM or non-ICM and LVEF ≤ 35% ($n = 1376$) | Rate control: β-blockers, digoxin, and recommendation for atrioventricular nodal ablation and pacemaker implantation when rate control targets were not achieved with drug therapy<br>Rhythm control: electrical cardioversion as necessary. AAD therapy in form of amiodarone, and either sotalol or dofetilide if required. Installation of permanent pacemaker was recommended if bradycardia prevented the use of AAD therapy<br>Continuation of OAC was recommended in both arms | Primary endpoint was time to death from cardiovascular causes. Secondary endpoints were death from any cause, stroke, worsening congestive heart failure, hospitalization, quality of life, cost of therapy, and a composite of death from cardiovascular causes, stroke, or worsening congestive heart failure | Rhythm control reduced neither the rate of death from cardiovascular cause ($P = 0.59$) nor the rate of death from any cause ($P = 0.73$), worsening heart failure ($P = 0.17$), or stroke ($P = 0.32$) |
| A4[33] | Paroxysmal AF resistant to at least one AAD ($n = 112$) | The aim was rhythm control achieved by AAD therapy or CA<br>AD therapy (either alone or in combination): amiodarone, quinidine, disopyramide, flecainide, propafenone, cibenzoline, dofetilide, sotalol<br>CA: PVI and bidirectional conduction block of the CTI; additional ablation lesions were made at the discretion of the operators | Freedom from AF during 1 year of FU | Superiority of CA compared with AAD therapy in maintenance of SR ($P < 0.0001$)<br>Significant improvement considering symptom score, exercise capacity, and quality of life in the ablation group |

*Continued*

**Table I** *Continued*

| Study (year of publication) | Patients | Treatment | Endpoints | Outcomes |
|---|---|---|---|---|
| | | Continuation of OAC was recommended in both arms | | High crossover rate from AAD group to CA (63%) compared with only 9% in the CA group ($P = 0.0001$) |
| CASTLE-AF (2018)[38] | Paroxysmal or persistent AF with ICM or non-ICM, LVEF ≤ 35% and ICD/CRT-D ($n = 363$) | CA: PVI; additional ablation lesions were made at the discretion of the operators<br>Medical treatment: Rate or rhythm control with a preference for rhythm control<br>Continuation of OAC was recommended in both arms | Composite of death from any cause or hospitalization for worsening heart failure | CA compared with medical treatment resulted in lower rates of death from any cause and lower rates of hospital admission for heart failure ($P = 0.006$), along with improving LVEF ($P = 0.005$) |
| CABANA (2019)[23] | Paroxysmal or persistent AF with one or more risk factors for stroke ($n = 2204$) | CA: PVI; additional ablation techniques were used at the discretion of the operators<br>Medical treatment: Rate or rhythm control with a preference for rate control<br>Continuation of OAC was recommended in both arms based on the $CHA_2DS_2$-VASc Score | Composite of death, disabling stroke, serious bleeding, or cardiac arrest | CA did not significantly reduce death, disabling stroke, serious bleeding, or cardiac arrest ($P = 0.3$)<br>Treatment effect of CA was affected by lower-than-expected event rates and high rates of therapeutic switches |
| EAST—AFNET 4 (2020)[5] | Recent-onset AF (diagnosed ≤1 year prior to enrolment, $n = 2789$) and stroke risk factors (approximating at $CHA_2DSVASC_2$ Score of ≥2) | Early rhythm control: CA with PVI and/or AAD therapy (amiodarone, dronedarone, flecainide, propafenone). Electrical cardioversion as necessary<br>Usual care: Preference for rate control. Rhythm control was only recommended when symptoms could not be controlled by optimal rate control<br>Continuation of OAC was recommended in both arms based on the $CHA_2DS_2$-VASc Score | Composite of cardiovascular death, stroke, and hospitalization due to worsening of heart failure or due to acute coronary syndrome | Early rhythm control therapy was associated with a lower risk of cardiovascular outcomes than usual care (21% hazard rate reduction, $P = 0.005$) |

AAD, antiarrhythmic drug; AF, atrial fibrillation; CA, catheter ablation; CRT-D, cardiac resynchronization therapy defibrillator; CTI, cavotricuspid isthmus; FU, follow-up; ICD, implantable cardioverter-defibrillator; ICM, ischaemic cardiomyopathy; non-ICM, non-ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; OAC, oral anticoagulation; PVI, pulmonary vein isolation; SR, sinus rhythm.

enrolled so far the largest randomized AF study,[23] were associated with high hopes. While the study underlined again the superiority of catheter ablation over antiarrhythmic drug therapy regarding the arrhythmia-free survival, there was no difference in the composite endpoint of death, disabling stroke, serious bleeding, or cardiac arrest between patients randomized to AF ablation and those randomized to antiarrhythmic drugs. Noteworthy, complication rates of antiarrhythmic therapy compared with catheter ablation for the treatment of AF did not differ in all of these studies. An excerpt from major studies of rate and rhythm control therapy for the treatment of atrial fibrillation is given in Table 1.

## Harry Crijns as a driver of clinical research to improve rhythm control therapy

It has long been known that AF causes severe and longer-lasting atrial damage ('AF begets AF'), as one of the first, seminal papers was entitled.[39] Taken seriously, this implies that an early initiation of rhythm control therapy should make restoration and maintenance of SR more effective. Indeed, approximately two-third of patients enrolled into ATHENA had their AF first diagnosed <12 months prior to enrolment, and almost three quarters were in SR at enrolment,[26] while most patients enrolled into RACE were in AF at enrolment, and many had a long history of AF. The importance of chasing rhythm control at an early stage of the disease was further supported by previous experiences with serial electrical cardioversion, intra-atrial defibrillation therapy, and, more recently, by favourable outcomes of early ablation of AF compared with delays in treatment.[40–42] Interestingly, the risk of AF-related complications, including death, is highest in the first year after the diagnosis of AF, and in a propensity-matched community sample, rhythm control by use of catheter ablation was associated with a reduced risk of stroke.[43] Therefore, as Harry Crijns put it, the time after the initial diagnosis of AF provides a window of opportunity to initiate rhythm control therapy.[44,45]

These considerations led to the design of the early treatment of AF for stroke prevention (EAST—AFNET 4) trial. Harry was one of the co-ordinating investigators involved from the start of the trial.[46] The trial combined several of the concepts that were developed after the disappointing results of the earlier rate vs. rhythm trials. These include

(1) enrolment of patients with early AF, diagnosed less than a year prior to enrolment,
(2) mandated continuation of anticoagulation and treatment of the cardiovascular conditions throughout the trial in all patients,
(3) providing guidance on the safe use and delivery of rhythm control therapy, and
(4) using both antiarrhythmic drugs, AF ablation, and their combination to achieve rhythm control.

The results speak for themselves: Early rhythm control therapy reduced a composite of cardiovascular death, stroke, and hospitalization for worsening of HF or acute coronary syndrome, by 21% (first primary outcome, absolute reduction 1.1 per 100 patient-years). Two hundred and forty-nine patients randomized to early rhythm control experienced an outcome event (3.9% per patient-year), compared with 316 patients randomized to usual care (5% per patient-year). Each component of the first primary outcome was numerically lower in the patients randomized to early rhythm control. The result was consistent across 19 predefined subgroups over a median follow-up time of 5.1 years. While early rhythm control therapy was associated with more adverse events related to rhythm control therapy, these events were rare (4.9% over the entire FU time) and the overall safety, estimated as a composite of death, stroke, or serious adverse events related to rhythm control therapy, was not different between groups (223 and 231 patients with events). Of note, the beneficial effects of early rhythm-control therapy were achieved without increasing the nights spent in hospital (2nd primary outcome parameter).

Thus, over almost three decades, Harry Crijns contributed to realizing the conceptual benefit of rhythm control therapy in patients with AF. It is almost easier to list the clinical trials without Harry's involvement than to list those which he co-designed and led.

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