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RAPID COMMUNICATIONS
Clinical trials

Short-term benefit of early rhythm control for atrial fibrillation: the EAST-AFNET 4 trial

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In acute medical care, rhythm control for atrial fibrillation (AF) is often not pursued based on perceived futility and potential side effects.[1,2] Systematic, early rhythm-control therapy reduces the long-term risk of adverse cardiovascular events compared with symptom-driven rhythm control based on a median follow-up of 5.1 years in the randomized, controlled *Early Rhythm-Control Therapy in Patients with Atrial Fibrillation* (EAST-AFNET 4) trial,[3] independent of AF-related symptoms[4] or heart failure status.[5] This effect is more pronounced in patients with multiple comorbidities.[6] A potential initial hazard of early rhythm control related to potential adverse events caused by antiarrhythmic drug initiation[7,8] or complications of electrophysiological interventions[9] could not be excluded during the design of EAST-AFNET 4. However, distinguishing whether beneficial effects are already found in the first few weeks after initiating rhythm control, or whether the outcome-reducing effects slowly accumulates over time, would have direct implications for the treatment of AF in patients with acute medical problems.

This *post hoc* analysis of EAST-AFNET 4 evaluated the short-term effects of early rhythm control therapy within the first 30 days after randomization, both in the overall study population and in patients with heart failure, which in EAST-AFNET 4 included patients at stable NYHA II or with a reduced left ventricular ejection fraction.[5] Outcomes were the primary outcome of EAST-AFNET 4 (time to first event of cardiovascular death, stroke, hospitalization with worsening of heart failure or acute coronary syndrome), individual components of the primary outcome, and the safety outcome (composite of death, stroke, or pre-specified serious adverse events of rhythm control therapy), as well as all-cause death, hospitalizations for worsening of heart failure, and nights spent in hospital. Randomized groups were compared within the intention-to-treat population using cause-specific Cox proportional hazard models for all time-to-event outcomes and mixed negative binominal model/mixed logistic regression for nights spent in hospital/the primary safety endpoint, adjusted for centre as a random effect. Patients randomized to early rhythm control transmitted telemetric ECGs regularly, and those closest to day 30 (range 10–30 days based on time point of treatment initiation) were used to assess rhythm at 30 days.

EAST-AFNET 4 enrolled patients with AF diagnosed within a year and with stroke risk factors (age > 75 years, prior stroke/transient ischaemic attack; or two of the following: age > 65 years, female sex, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease, left ventricular hypertrophy).

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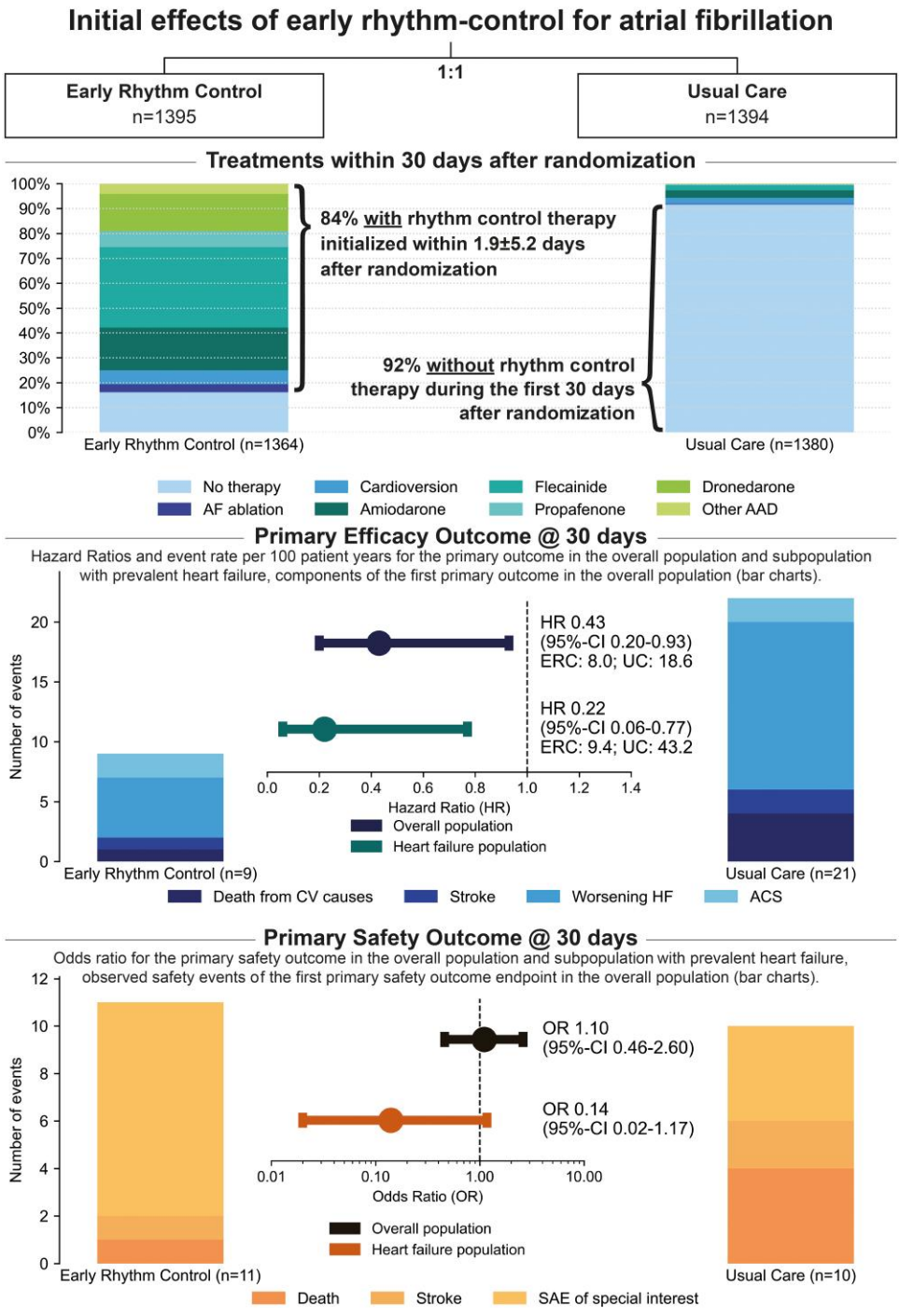

Figure 1 Use of treatments, primary outcomes, and safety outcomes within 30 days after randomization in the overall study cohort from the EAST-AFNET 4 trial

All randomized patients received optimal care of cardiovascular conditions and anticoagulation.[2,10] Patients randomized to early rhythm control received cardioversion, antiarrhythmic drugs, or ablation therapy. Patients randomized to usual care received rate-control therapy only, later combined with symptom-directed rhythm-control therapy.[3]

Within 30 days after randomization, patients randomized to early rhythm control received treatment within 1.9 ± 5.2 days which included antiarrhythmic drugs (1100/1364; 80.6%), cardioversion (79/1364; 5.8%), and AF ablation (44/1364; 3.2%) (*Figure 1*). In patients randomized to usual care, 1265/1380 (91.7%) patients did not receive rhythm control within 30 days after randomization. Only 95/1380 (6.9%) usual care patients were treated with antiarrhythmic drugs, 34/1380 (2.5%) patients with cardioversion, and 4/1380 (0.3%) patients with catheter ablation, overall initiated 6.6 ± 9.3 days after randomization. Although baseline mean heart rate was not different between groups (65.5 ± 13.3 b.p.m. in early rhythm control; 65.2 ± 11.9 in usual

care), use of rate-control therapy was higher in usual care (89.4% vs 79.8%). A primary outcome event occurred in 9/1395 patients randomized to early rhythm-control (8 events per 100 patient-years) and in 21/1394 patients in the usual care group [18.6 events per 100 patient-years; hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.20–0.93; *Figure 1*] within 30 days after randomization. A primary safety outcome occurred in 11/1395 (0.8%) patients with early rhythm-control and in 10/1394 (0.7%) patients with usual care within that time range (OR 1.10, 95% CI 0.46–2.60; *Figure 1*). Deaths were observed in 1/1395 patient randomized to early rhythm-control and in 4/1394 patients randomized to usual care (0.9 deaths per 100 patient-years vs 3.5 per 100 patient-years, HR 0.25, 95% CI 0.03–2.24). Early rhythm-control reduced the outcome of hospitalization for worsening heart failure (early rhythm-control 4.5 events/100 patient-years; usual care 12.4 events/100 patient-years; HR 0.36, 95% CI 0.13–0.99) but not nights spent in hospital (0.3 ± 0.4 vs 0.2 ± 0.4 nights, IRR 1.23, 95% CI 1.05–1.44). In patients randomized to early rhythm control with definable rhythm at 30 days (1002/1394), presence of sinus rhythm increased from 55.2% at baseline to 76.8% at 30 days.

In EAST-AFNET 4, 798/2789 (28.6%) patients had prevalent heart failure of which 396 patients were randomized to early rhythm-control therapy and 402 patients were randomized to usual care. Within 30 days after randomization, a primary outcome occurred in 3/396 patients with prevalent heart failure randomized to early rhythm-control (9.4 per 100 patient-years) and in 14/402 patients with usual care (43.2 per 100 patient-years, HR 0.22, 95% CI 0.06–0.77; *Figure 1*). A primary safety event occurred in 1/396 (0.3%) patients randomized to early rhythm-control and in 7/402 (1.7%) patients randomized to usual care within 30 days after randomization (OR 0.14, 95% CI 0.02–1.17; *Figure 1*). Treatment use was comparable with treatment within 30 days observed in the overall population (80.7% vs 9.8% antiarrhythmic drugs, 8.5% vs 3.8% cardioversion, and 3.3% vs 1.0% catheter ablation).

This exploratory analysis suggests immediate beneficial effects of early rhythm-control therapy within 30 days after randomization, including a lower incidence of the primary outcome, fewer deaths, and a reduced composite of death or heart failure hospitalization. The findings were consistent in the overall population and in the population with heart failure (mainly heart failure with preserved ejection fraction[6]). Importantly, early rhythm-control therapy seems to induce an early risk reduction with a favourable safety profile in the risk of worsening heart failure. This supports its early implementation in patients at risk of heart failure or with acute and advanced heart failure. Future studies are needed (i) to clarify the exact role and mediators of the early effect of early rhythm-control therapy in these patient populations and (ii) specifically to evaluate the early effects of rhythm-control therapy in the acute setting.

Declarations

Disclosure of Interest

J.O. received travel grants from Abbott and Abiomed and is co-founder and managing director of IDM gGmbH, a 100% non-profit subsidiary of the University Medical Center Hamburg-Eppendorf. J.O. received research grants from German Heart Foundation, German Center for Cardiovascular Research, University of Hamburg, and German Federal Ministry of Education and Research. A.S. received research support for statistical analyses from AFNET, the European Union, Biotronik, and Adrenomed AG to the institution. K.B. does not disclose any personal fees from third parties. A.J.C. received consulting fees from Bayer, Pfizer/BMS, Daiichi Sankyo, Acesion, InCarda Therapeutics, Abbott, Boston Scientific, Medtronic, HUYA Bio, and Biosense Webster and lecture honoria from Bayer, Sanofi, and Menarini. H.J.G.M.C. discloses advisory board fees from InCarda Therapeutics, Roche Diagnostics, Daiichi Sankyo, Sanofi, Acesion, and AtriCure and speaker fee from Medtronic. L.E. received consulting fees from Boston Scientific and lecture fees from various medical companies. L.E. received research support from the German Heart Foundation. L.F. received institutional research grants from EU 633196 (CATCH ME) and EU 965286 (MAESTRIA), British Heart Foundation (AA/18/2/34218), German Center for Cardiovascular Research supported by the German Ministry of Education and Research (DZHK), and several biomedical companies active in the field of research. L.F. is listed as inventor on two issued patents held by the employing institution (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). A.G. received consulting fees from Daiichi Sankyo and payment or honoraria from Daiichi Sankyo, Bayer, Boehringer, Pfizer, Bristol-Meyers Squibb, Boston Scientific, and Medtronic. A.G. received research grants from EU 965286 (MAESTRIA). M.J. received consulting fees from Bristol-Myers Squibb. M.D.L. was supported by the Research Promotion Fund of the Faculty of Medicine (Hamburg, UKE, 'Clinician Scientist Program') and received a research grant from Farapulse and a travel grant from Biosense Webster. C.M. received research funding from German Center for Cardiovascular Research (promotion of women scientists), Deutsche Stiftung für Herzforschung, Dr. Rolf M. Schwiete Stiftung, NDD AG, and Loewenstein Medical; consulting fees from Boehringer Ingelheim and Novo Nordisk; and lecture honoraria and travel grants from Novo Nordisk, AstraZeneca, Novartis, Boehringer Ingelheim/Lilly, Bayer, and Edwards. A.M. received consulting fees from Medtronic and Biosense Webster and received lecture honoraria or travel support from Medtronic, LifeTech, Biosense Webster, Daiichi Sankyo, Boston Scientific, Haemonetics, Bayer, Bristol Meyers Squibb, AtriCure, and Pfizer. A.R. received consulting fees from Medtronic, KODEX-EPD, Biosense Webster, Boston Scientific, and AtriCure, as well as travel grants and lecture fees from Medtronic, CardioFocus, Biosense Webster, Abbott, Boehringer Ingelheim, Philips KODEX-EPD, Ablamap, Bayer, Novartis, LifeTech, Boston Scientific, AtriCure, and Lilly, and serves as the speaker elect in the German Society of Cardiology's working group for electrophysiology. U.S. reports grants of the Dutch Heart Foundation (CVON2014-09, RACE V Reappraisal of Atrial Fibrillation: Interaction between hyperCoagulability, Electrical remodeling, and Vascular Destabilisation in the Progression of AF, and Grant number 01-002-2022-0118, EmbRACE: Electro-Molecular Basis and the theRapeutic management of Atrial Cardiomyopathy, fibrillation and associated outcomEs), EU 965286 (MAESTRIA). U.S. received consultancy fees or honoraria from the Università della Svizzera Italiana (USI, Switzerland) and Roche Diagnostics (Switzerland). U.S. was supported by a grant from EP Solutions Inc. (Switzerland) and is co-founder and shareholder of YourRhythmics BV, a spinoff company of the University Maastricht. R.B.S. has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme under the grant agreement no. 648131, from the European Union's Horizon 2020 research and innovation programme under the grant agreement no. 847770 (AFFECT-EU), from the European Union's Horizon Europe research and innovation programme under the grant agreement ID: 101095480, German Center for Cardiovascular Research (DZHK e.V.) (81Z1710103 and 81Z0710114), German Ministry of Research

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Data Availability

Anonymised data may be provided upon reasonable request. Please contact AFNET info: info@kompetenznetzvorhofflimmern.de.

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Ethical Approval

The protocol of EAST-AFNET 4 was approved by the ethics review boards of all the institutions involved. Written informed consent was provided by all patients who participated in the trial: *Ethikkommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster, 09/02/2011, ref: 2010–274-f-A*.

Pre-registered Clinical Trial Number

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