Transforming clinical research by involving and empowering patients— the RATE-AF randomized trial

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Title: Transforming clinical research by involving and empowering patients – the RATE-AF randomised trial

Standfirst: Designed and managed with the support of patient and public representatives, the RATE-AF trial is the first head-to-head randomised trial of digoxin vs beta-blockers in patients with atrial fibrillation and symptoms of heart failure.

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[word count = 1038]

The RAte control Therapy Evaluation in permanent Atrial Fibrillation (RATE-AF) trial was designed as a pragmatic, healthcare-embedded clinical trial to address the concerns of patients and improve quality of life.[1] With the main results recently published in *JAMA*[2], RATE-AF has demonstrated how Patient and Public Involvement (PPI) in trial design and management can provide new opportunities and generate a robust evidence-base to guide routine clinical management.

Evidence for a Patient and Public involvement approach

"Research being carried out 'with' or 'by' members of the public (including patients and carers) rather than 'to', 'about' or 'for' them" is the definition of Patient and Public involvement (www.invo.org.uk). Using PPI in trial development and management has the potential to augment patient recruitment in clinical trials, addressing the fact that one third of clinical trials fail to reach their recruitment target. In a meta-analysis of 19 studies including a total of 178,921 participants, 11 out of 21 PPI interventions increased enrolment rates. In

the 7 randomised trials, the odds ratio (OR) of a patient enrolling was 1.16 compared to no PPI intervention (95% prediction interval 1.25- 2.80; p=0.04 with no heterogeneity).[3] Across all study types, an even more substantial improvement in recruitment was demonstrated if the PPI member had the health condition of interest (OR 3.14, 1.89-5.22; versus 1.07, 0.74-1.53 without the condition).[3] Although the authors found no evidence of significant publication bias, data were insufficient to address whether participant retention was improved. Nevertheless, this adds to growing information that PPI, if properly supported (see **Figure 1**) can assist in the deployment of a clinical trial, ethical approval, avoidance of protocol amendments, enhanced participant adherence, and lead to reduced cost.[4] PPI is of particular importance in data-intensive healthcare research, where informed consent and privacy are fundamental to good governance and acceptance by potential participants.[5] The ESC is actively involved in this critical area of big data research (www.escardio.org/bigdata). Finally, PPI provides a clear route to embedding the patient voice into clinical research, leading to benefit for all stakeholders.

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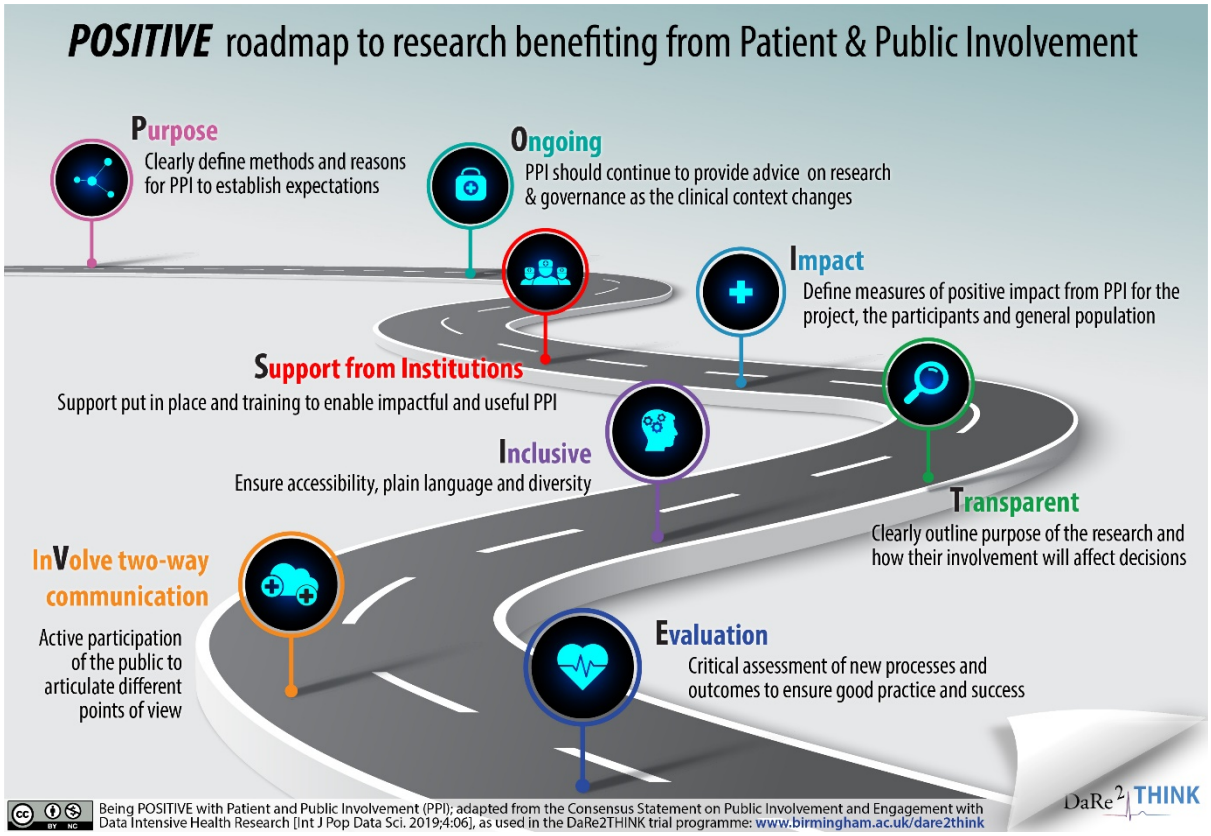
Figure 1: Being POSITIVE with Patient and Public Involvement.



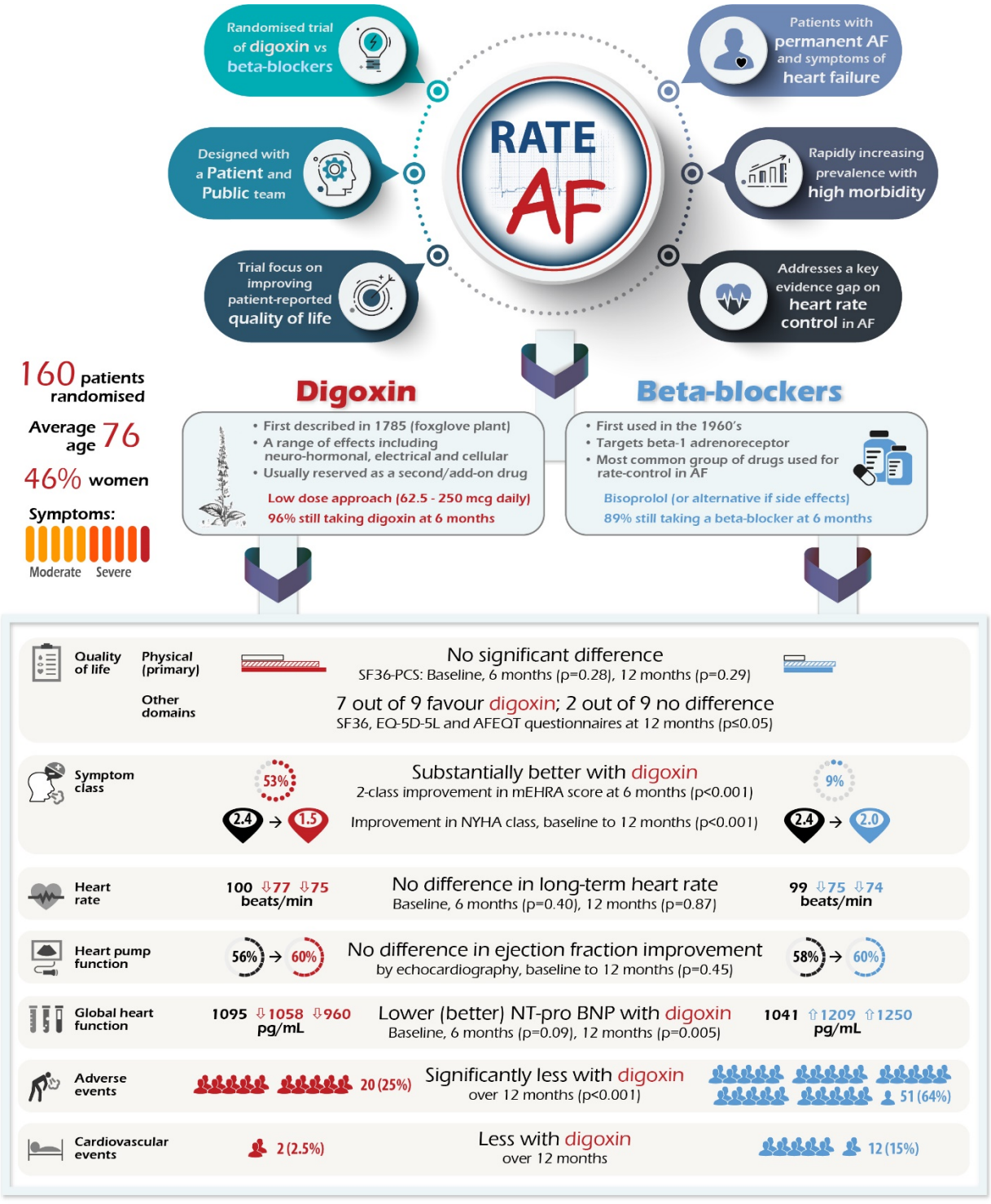
The RATE-AF trial

The RATE-AF trial was a prospective, randomised, open-label, blinded end-point trial addressing a major evidence gap in the management of AF, the issue of heart rate control.[1] Previous studies were either observational (ignoring the fact that digoxin is often used as second-line drug and therefore given to sicker patients[6]), or only demonstrating short-term outcomes such as acute change in heart rate. In contrast, the RATE-AF trial randomised patients to either low-dose digoxin or beta-blockers, with outcomes at 6 and 12 months.[1] One hundred and 60 patients aged 60 years or older with permanent AF and at least New York Heart Association class II dyspnoea were recruited to the trial, with key findings summarised in **Figure 2**. There was no difference in the primary outcome of the physical component of quality of life, no difference in long-term heart rate control, and no

deterioration in left-ventricular ejection fraction comparing low-dose digoxin with beta-blockers.

Patients randomised to the digoxin group had significantly better improvement in modified European Heart Rhythm Association (mEHRA) functional class, with 53% reporting a two-class improvement with digoxin at 6-months versus 9% for beta-blockers ($p<0.001$). A significant reduction in NTpro-B-type natriuretic peptide at 12-months was seen in the digoxin group ($p=0.005$), with substantially less adverse events compared to beta-blockers (29 events [25% of patients] versus 142 events [64% of patients]; $p<0.001$). Many of the patient-reported elements of general and treatment-specific quality of life also favoured the group randomized to digoxin.

Insert image with caption: Figure 2: Key findings from the RATE-AF trial



For full results, please refer to Kotecha et al, JAMA 2020;324:2497-508.

Image of the foxglove plant is copied from the 1785 book "An Account of the Foxglove and Some of its Medical Uses" by William Withering (publisher Swinney: Birmingham).

AF = atrial fibrillation; AFEQT = Atrial Fibrillation Effect on QualiTy-of-life questionnaire; EQ-5D-5L = EuroQol five-dimension five-level questionnaire; mEHRA = modified European Heart Rhythm Association class; NT-pro BNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association class; SF36-PCS = Short Form 36 Physical Component Summary score.

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Evolution of RATE-AF with patient and public involvement

The PPI team made considerable input to the design of the trial; as advocates for patients with AF they impressed the importance of patient well-being as a priority, establishing the primary outcome as patient-reported quality of life. The PPI team enhanced recruitment, for example by producing a YouTube participant video, and boosted retention of participants (only 3 patients [1.9%] in the trial withdrew). They also led the development of all patient-facing material, enabling clear and explanatory consent forms and information leaflets. This allowed participants to make truly informed consent and improved their adherence to study medications. Plain English summaries of the main results have led to dissemination to a wider audience, particularly for patients with AF in the community and their general practitioners. As members of the Trial Steering Committee, PPI input was essential for the progress of the trial, such as strategies to accelerate recruitment and the development of sub-studies. This included embedded studies on: (1) Wearable devices, where the PPI team helped to implement technology despite the older population being recruited; (2) Basic science experiments on cellular and mass-spectrometry endpoints; and (3) PPI-led qualitative studies to understand the importance of quality of life in the routine clinical assessment of patients with AF.[7]

Mary's viewpoint as a patient on designing and managing RATE-AF

"My involvement with the RATE-AF trial began after I was diagnosed and treated for paroxysmal atrial fibrillation. My fellow PPI team members and I have contributed to the design of the study, successful application for funding, trial steering group meetings and now the final rewarding results of many years of work. We also led focus groups exploring quality of life in patients with atrial fibrillation – which we went on to write up, publish and

present at the International Society of Quality of Life Research conference where we were awarded Patient Research Partner Scholarships.

It was these focus groups which gave me the most satisfaction - designing and running them, listening to patients talking about their quality of life, the neglect they felt at usual health consultations, and the impact that the trial was having on them. Many patients felt we had boosted their confidence and ability to self-manage their AF."

Future perspectives

The involvement of patients, carers and the public (and indeed anyone outside the usual clinical-academic framework), has the potential to improve the basis for clinical trials, support recruitment and retention of participants, and lead to more robust, and better targeted evidence generation. PPI is now commonplace in stakeholder meetings, the generation of clinical practice guidelines and efforts at dissemination. Being a mandatory part of developing and managing research studies internationally would seem the next sensible step to reducing the burden of cardiovascular disease.

Insert images in author boxes

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On behalf of the RATE-AF Investigators (see Appendix)

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The RATE-AF trial and patient and public involvement were funded by the UK National Institute for Health Research (NIHR; CDF-2015-08-074).

Acknowledgements:

Online supplementary Appendix: The RATE-AF team

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Online supplementary Appendix: The RATE-AF team

Name	Role/Position	Institution (current)
Patient Public Involvement representatives		
Sandra Haynes	Patient and Public Involvement team	n/a
Jacqueline C Jones	Patient and Public Involvement team	
Mary Stanbury	Patient and Public Involvement Lead	
Trial Management Team and Investigators		
Dr Karina V Bunting	PhD Fellow & Research Assistant; Senior Cardiac Physiologist	Institute of Cardiovascular Sciences, University of Birmingham (UoB) & University Hospitals Birmingham, NHS Foundation Trust (UHBFT), UK
Prof Melanie J Calvert	Professor of Outcomes Methodology	Institute of Applied Health Research, UoB, UK
Prof Jonathan J Deeks	Professor of Biostatistics	Birmingham Clinical Trials Unit, UoB, UK
Patience Domingos	Research Nurse	Sandwell & West Birmingham Hospitals NHS Trust & UHBFT, UK
Dr Simrat K Gill	PhD Fellow; Specialist Cardiology Registrar	Institute of Cardiovascular Sciences, UoB & UHBFT, UK
Dr Margaret Grant	Trial Manager	Birmingham Clinical Trials Unit, UoB, UK
Dr Michael Griffith	Principal Investigator; Consultant Electrophysiologist	UHBFT, UK
Emma Hayes	Trial Manager	Birmingham Clinical Trials Unit, UoB, UK
Dr Susan Jowett	Senior Lecturer in Health Economics	Institute of Applied Health Research, UoB, UK
Prof Paulus Kirchhof	Professor of Cardiovascular Medicine	Institute of Cardiovascular Science, UoB & UHBFT, UK & Hamburg Center for Cardiovascular research
Prof Dipak Kotecha	Chief Investigator; Professor of Cardiology & Cardiac Imaging	Institute of Cardiovascular Sciences, UoB & UHBFT, UK
Prof Gregory YH Lip	Principal Investigator; Professor of Cardiovascular Medicine	University of Liverpool and Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool, UK
Dr Jonathan Mathers	Senior lecturer in Qualitative and Mixed Methods Research	Institute of Applied Health Research, UoB, UK
Samir Mehta	Trial Statistician	Birmingham Clinical Trials Unit, UoB, UK
Sukhi Sehmi	Trial Manager	Birmingham Clinical Trials Unit, UoB, UK
Dr Gemma Slinn	Trials Unit Team Leader	Birmingham Clinical Trials Unit, UoB, UK
Dr Richard P Steeds	Consultant Cardiologist and Head of Cardiac Imaging	UHBFT & Institute of Cardiovascular Sciences, UoB, UK
Dr Victoria Stoll	Specialist cardiology registrar and Clinical Lecturer	Institute of Cardiovascular Sciences, UoB & UHBFT, UK
Prof Jonathan N Townend	Principal Investigator; Professor of Cardiology	UHBFT & Institute of Cardiovascular Sciences, UoB, UK
Dr Rebekah Wale	Trial Manager	Birmingham Clinical Trials Unit, UoB, UK
Hannah Watson	Trial Manager	Birmingham Clinical Trials Unit, UoB, UK
Trial Oversight Committees		
Prof A John Camm	Independent Chair of the Trial Steering Committee	St George's University of London, London, UK
Prof Kazem Rahimi	Independent Chair of the Data Monitoring Committee	University of Oxford, Oxford UK
Dr Victoria Y Strauss	Independent Statistician	University of Oxford, Oxford, UK

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