Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Trial funding & oversight

RATE-AF was initiated and coordinated by the Institute of Cardiovascular Sciences and the Birmingham Clinical Trials Unit at the University of Birmingham, UK. The study was funded by the National Institute for Health Research (NIHR) as part of a Career Development Fellowship to the Chief Investigator (DK; CDF-2015-08-074). There was no industry funding for any part of this trial. Oversight was performed by a Trial Steering Committee, which included the Patient and Public Involvement team, an independent Chair and representatives of the RATE-AF Trial Management Group. An independent Data Monitoring Committee met five times during the course of the trial and recommended continuation at each time-point after reviewing blinded data.

Recruitment sites

The trial was designed to mimic routine clinical care and involved referral for rate-control within the UK National Health Service (NHS). Patients were recruited from General Practices across the West Midlands region, and three hospital sites in Birmingham (Queen Elizabeth Hospital, City Hospital and Heartlands Hospital) from December 2016 to October 2018.

Baseline and follow-up assessment

Permanent AF was characterized as a clinical decision for rate control with no plans for cardioversion, anti-arrhythmic drugs or ablation, as per guidelines.[1] All patients were asked to pause any current rate control therapy for 24 hours prior to being randomized, so that the allocated therapy could be started on the morning immediately following the baseline visit. Patients were expected to be anticoagulated according to their clinical risk of thromboembolism. All study visits took place in the NIHR/Wellcome Trust Clinical Research Facility at the Queen Elizabeth Hospital,

Birmingham. At baseline, participants underwent 12-lead ECG then echocardiography to confirm AF, followed by completion of patient-reported quality of life (QoL) questionnaires, clinical assessment, supervised 6-minute walk distance (6MWD), and blood tests including NTpro B-type natriuretic peptide (NTproBNP). Patients attended uptitration visits (see details below) in order to attain a heart rate at rest of ≤100bpm, following guidance that lenient control of heart rate in AF is preferential for most patients.[1,2] All participants were reviewed at 6 and 12-months following their baseline visit. Patient-reported QoL questionnaires were performed first to reduce bias, and were self-administered except for those patients with visual or physical impediment. This was followed by 12-lead ECG, clinical assessment, 6MWD and NTproBNP. Repeat echocardiography was only performed at 12-months. During follow-up, the trial team took on responsibility for general cardiovascular care, including testing and management of hypertension, coronary artery disease, cardiomyopathy or heart failure according to usual practice.

Ethnicity data

Randomized patients were asked to self-declare their ethnicity based on the code list for the UK 2011 Census, with an option to decline available. UK National Health Service organizations are mandated to use ethnic monitoring questions to monitor patients, service users and staff against the protected characteristics of the Equality Act 2010.

Intervention details & uptitration

The Birmingham Clinical Trials Unit was responsible for the random allocation sequence and assignment of the intervention, using the methods described in the main text. Drug therapy was initiated the immediate day after their baseline visit.

In the digoxin arm, patients were commenced on low-dose digoxin once-daily, and any beta-blockers were stopped. We used a simplified approach in these patients, whereby a clinically-

appropriate daily dose was chosen by the clinician in the range of at 62.5 to 250mcg based on patient size and any known renal impairment (default 125mcg). Twice this amount was given as a loading dose on the first day of treatment only, and thereafter the patient was asked to continue on the usual daily dose until review at 3-4 weeks when uptitration was considered based on the response in terms of heart rate and symptoms. A serum digoxin level was taken to ensure safety. In the beta-blocker arm, bisoprolol was commenced at a dose of 1.25 to 15mg once-daily, determined by the clinician in the context of any prior beta-blocker use (default 2.5mg). Bisoprolol was chosen as the beta-blocker of choice as this is the most widely prescribed in the UK; in patients randomized to bisoprolol but with known intolerance, an alternate beta-blocker was acceptable (nebivolol, carvedilol or metoprolol). There were no patients currently on digoxin at the time of commencement. Uptitration by the clinician took account of response in terms of heart rate and symptoms; for patients with adverse events, switching to an alternate beta-blocker was acceptable.

In both groups, clinicians and patients had the option of additional uptitration visits as needed to control heart rate and symptoms from AF. In the digoxin group, the mean number of visits was 1.4 (SD 0.6; range 1-3). In the beta-blocker group, the mean was 1.5 visits (SD 0.9; range 1-6). Combination therapy was acceptable in patients with a persistent heart rate >100 beats/min according to a protocol flowchart.[3] After uptitration was completed, a 24-hour ambulatory ECG was performed to confirm adequate rate-control and ensure safety with regards to pauses or any heart block; any suggested changes needed in rate-control treatment were communicated to Primary Care physicians, who were thereafter responsible for drug prescription.

Quality of life tools and scoring

Quality of life (QoL) questionnaires were completed on paper forms in the following order: EQ-5D-5L, SF36 then AFEQT. These were then transferred to the Birmingham Clinical Trials Unit, who independently uploaded QoL data into the case report database. Scoring was performed by the

trials unit only after the study was completed. We hypothesized, based on previous literature, that physical domains would likely respond to heart rate control, and 6-months was chosen due to the assumed impact of other comorbidities over longer periods.

SF36 was scored according to eight domains, and the Physical and Mental Component Summaries (PCS and MCS) derived from these domains. In brief, the answer from each SF36 question is numerically coded and then summed with other questions to form the domain scores with a range of 0 to 100, with higher scores representing better self-reported health. These are then multiplied by a population-based factor and summed to generate the PCS and MCS, which also have a range of 0 to 100. Similar to other instruments, anchor-based analysis suggests a minimal clinically important difference (MCID) of 0.5 SD.[4] This distributional criterion encompasses the variability in MCID observed across different disease populations. Absolute values in heart failure are between 4.1 and 9.2 when anchored to mortality[5] (see **Supplement 3, eTable 6** for studies in patients with AF). In the Statistical Analysis Plan, domain and summary scores were primarily analyzed using raw values; for ease of interpretation and comparison, these are also presented normalized to a mean score of 50 according to UK-based survey data.[6]

The EuroQol EQ-5D-5L questionnaire includes: (1) a Visual Analogue Score, a mark placed by the patient on a scale of 0 (worst health that can be imagined) to 100 (best health that can be imagined); and (2) the Summary Index Score, which is derived from a five-level scale for 5 domains of general QoL and converted to an index score with a range of 0 (death) to 1 (complete health). Results are mapped to the England value set for EQ-5D-3L[7] in accordance with guidance from the National Institute for Health Research, with an average MCID of 0.18.[8] The Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire was scored as described[9], by generating an overall score and then subscales for symptoms, daily activities, treatment concern and treatment satisfaction. All scores range from 0 (complete disability) to 100 (highest level of QoL). Using the EHRA score as an anchor, a 5-point change in AFEQT scores are expected to be clinically important.[10]

QoL domains were blinded; although participants completed the forms, they were not aware of which questions constituted each domain or component summary, investigators were not involved in scoring, and the scoring itself requires complex calculation (for example, factorization and normalization). The only exception to this was the EQ-5D-5L Visual Analogue Score, which is clearly visible to patients and research staff.

Echocardiography protocol

All patients underwent transthoracic echocardiography at baseline and 12-months using a Philips EPIQ 7 and X5-1 transducer by an accredited echocardiographer. After optimization, recorded images were stored with no identifiable features and given a distinct, random, alphanumeric code. Blinded analysis of images was performed a minimum of 3 months after the scan date. To improve reproducibility in the context of AF, echocardiographic parameters were derived by using a more physiological approach to imaging.[11] The index-beat method selects cardiac cycles where the difference in preceding and pre-preceding RR intervals are <60 msec.[12] Three index-beats were averaged for each patient to determine LVEF and E/e'. A composite of diastolic indices was used to determine the presence of diastolic dysfunction, based on an average E/e' ≥15, or if <15 then two or more of isovolumic relaxation time ≤65ms, mitral E deceleration time ≤120ms, average E/e' ≥11 or pulmonary vein diastolic deceleration time ≤220ms.

Patient and Public Involvement (PPI)

PPI was integrated throughout the trial, from conception to closure, and included PPI-led focus groups of patients with AF to understand the importance and measurement of QoL.[13] PPI members received funding according to NIHR INVOLVE guidance (https://www.invo.org.uk/).

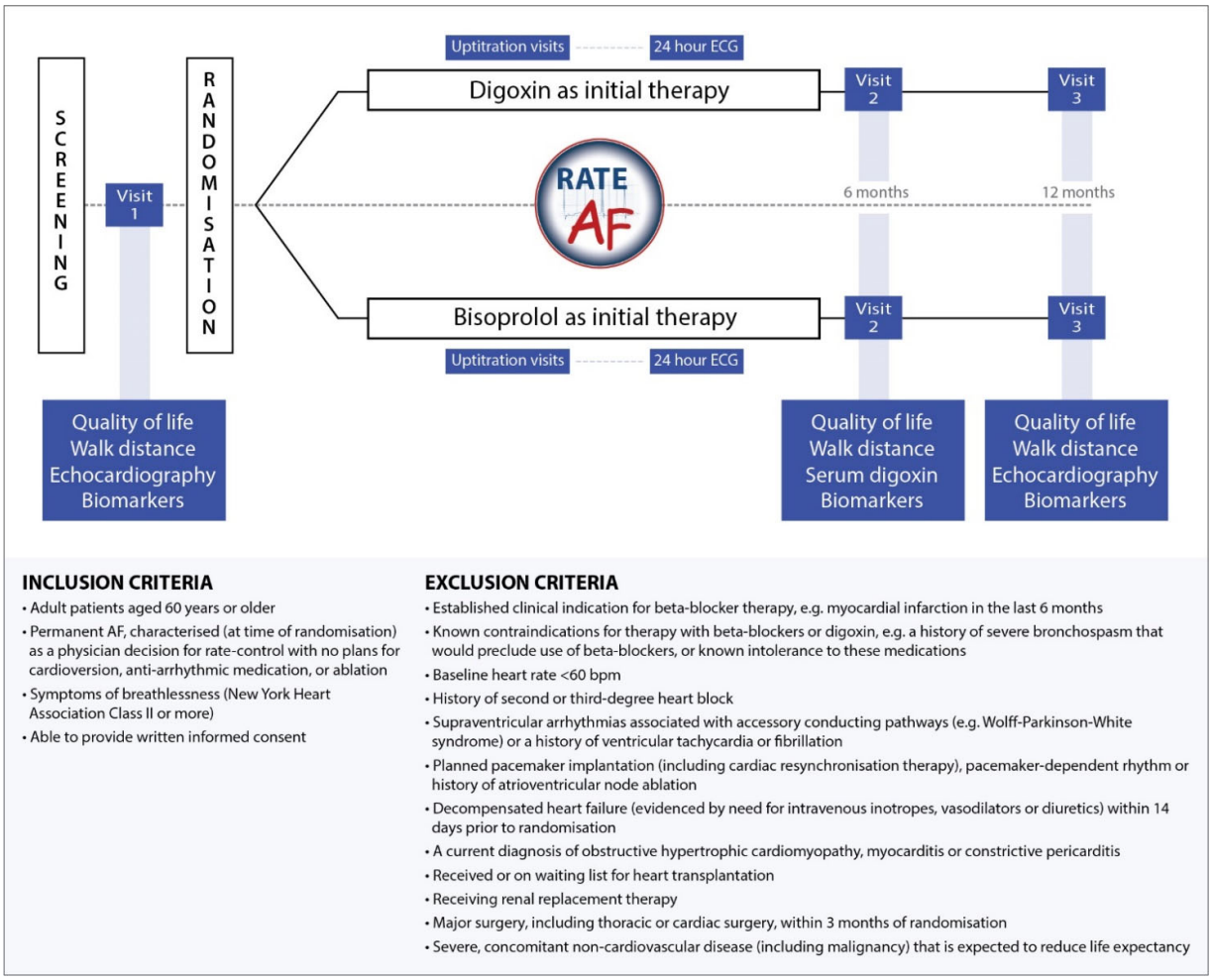
Software tools

Echocardiography analysis was performed on Q-station version 3.5 (Philips Healthcare, Massachusetts). Sankey diagrams were created using an open source tool available at http://sankeymatic.com and edited using Illustrator version 23.1 (Adobe Inc., California).

Guidance statements

The RATE-AF protocol was developed in accordance with the Standard Protocol Items for Randomized Trials (SPIRIT) statement[14], and reported according to the Consolidated Standards of Reporting Trials (CONSORT) Statement[15] and the patient-reported outcomes extension.[16]

eFigure 1. RATE-AF trial flowchart and selection criteria



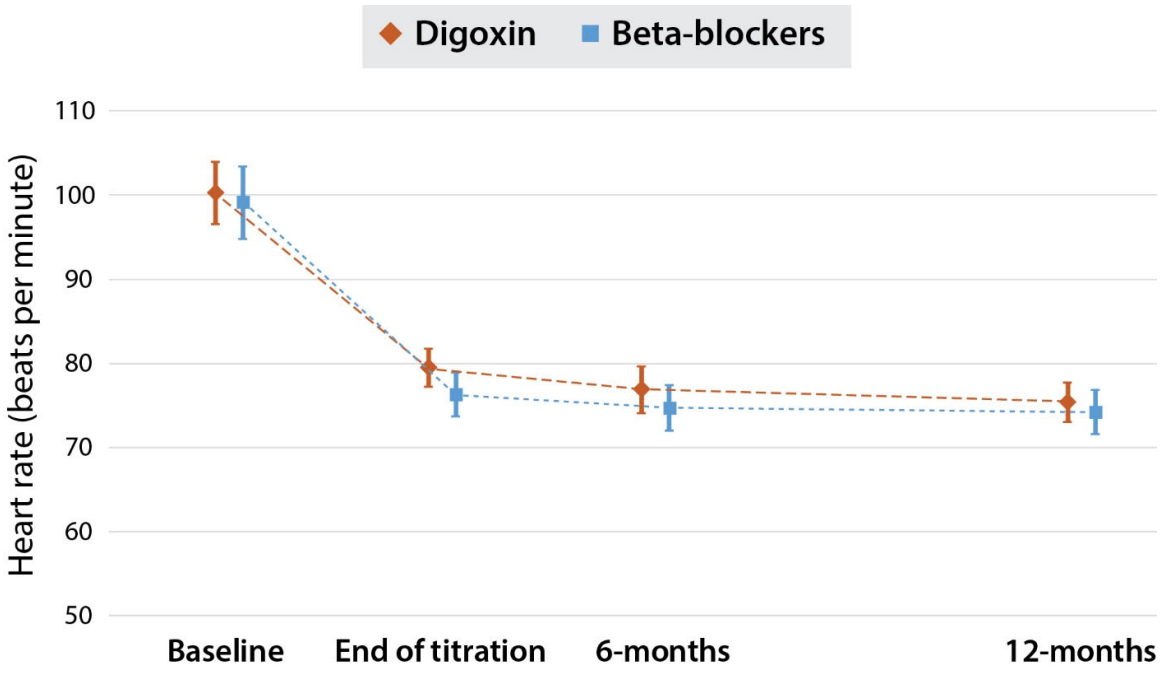
INCLUSION CRITERIA

- Adult patients aged 60 years or older
- Permanent AF, characterised (at time of randomisation) as a physician decision for rate-control with no plans for cardioversion, anti-arrhythmic medication, or ablation
- Symptoms of breathlessness (New York Heart Association Class II or more)
- Able to provide written informed consent

EXCLUSION CRITERIA

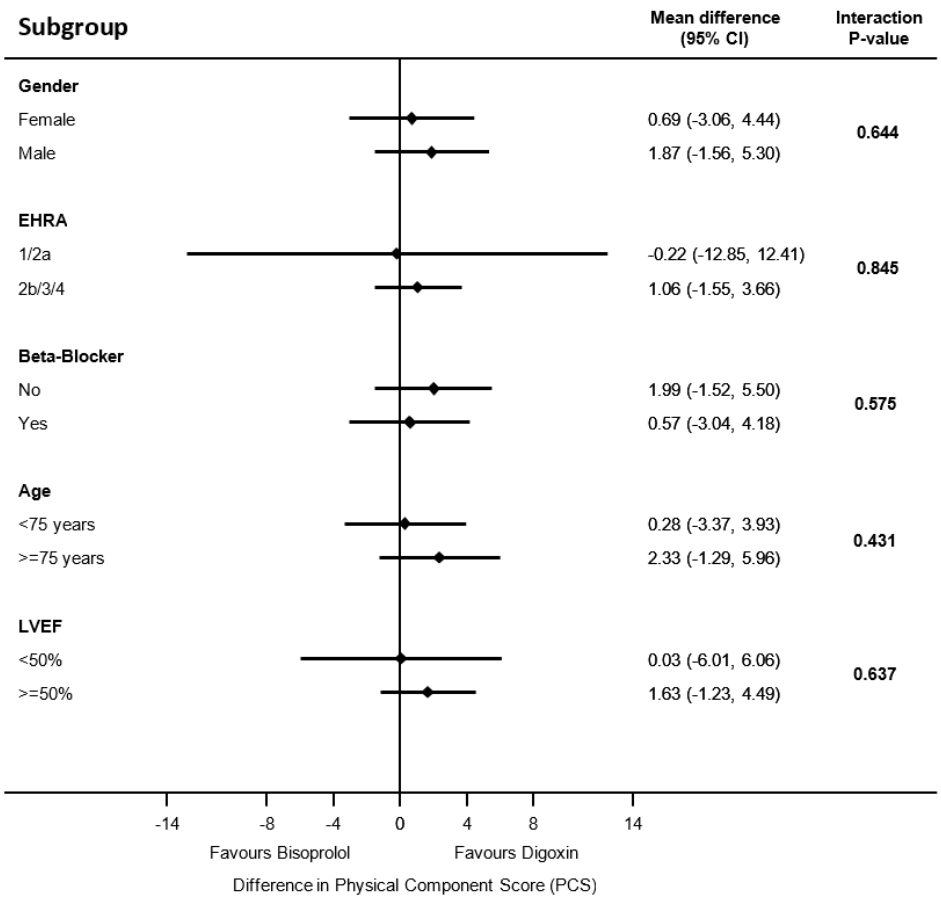
- Established clinical indication for beta-blocker therapy, e.g. myocardial infarction in the last 6 months
- Known contraindications for therapy with beta-blockers or digoxin, e.g. a history of severe bronchospasm that would preclude use of beta-blockers, or known intolerance to these medications
- Baseline heart rate <60 bpm
- History of second or third-degree heart block
- Supraventricular arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome) or a history of ventricular tachycardia or fibrillation
- Planned pacemaker implantation (including cardiac resynchronisation therapy), pacemaker-dependent rhythm or history of atrioventricular node ablation
- Decompensated heart failure (evidenced by need for intravenous inotropes, vasodilators or diuretics) within 14 days prior to randomisation
- A current diagnosis of obstructive hypertrophic cardiomyopathy, myocarditis or constrictive pericarditis
- Received or on waiting list for heart transplantation
- Receiving renal replacement therapy
- Major surgery, including thoracic or cardiac surgery, within 3 months of randomisation
- Severe, concomitant non-cardiovascular disease (including malignancy) that is expected to reduce life expectancy

eFigure 2. Change in heart rate



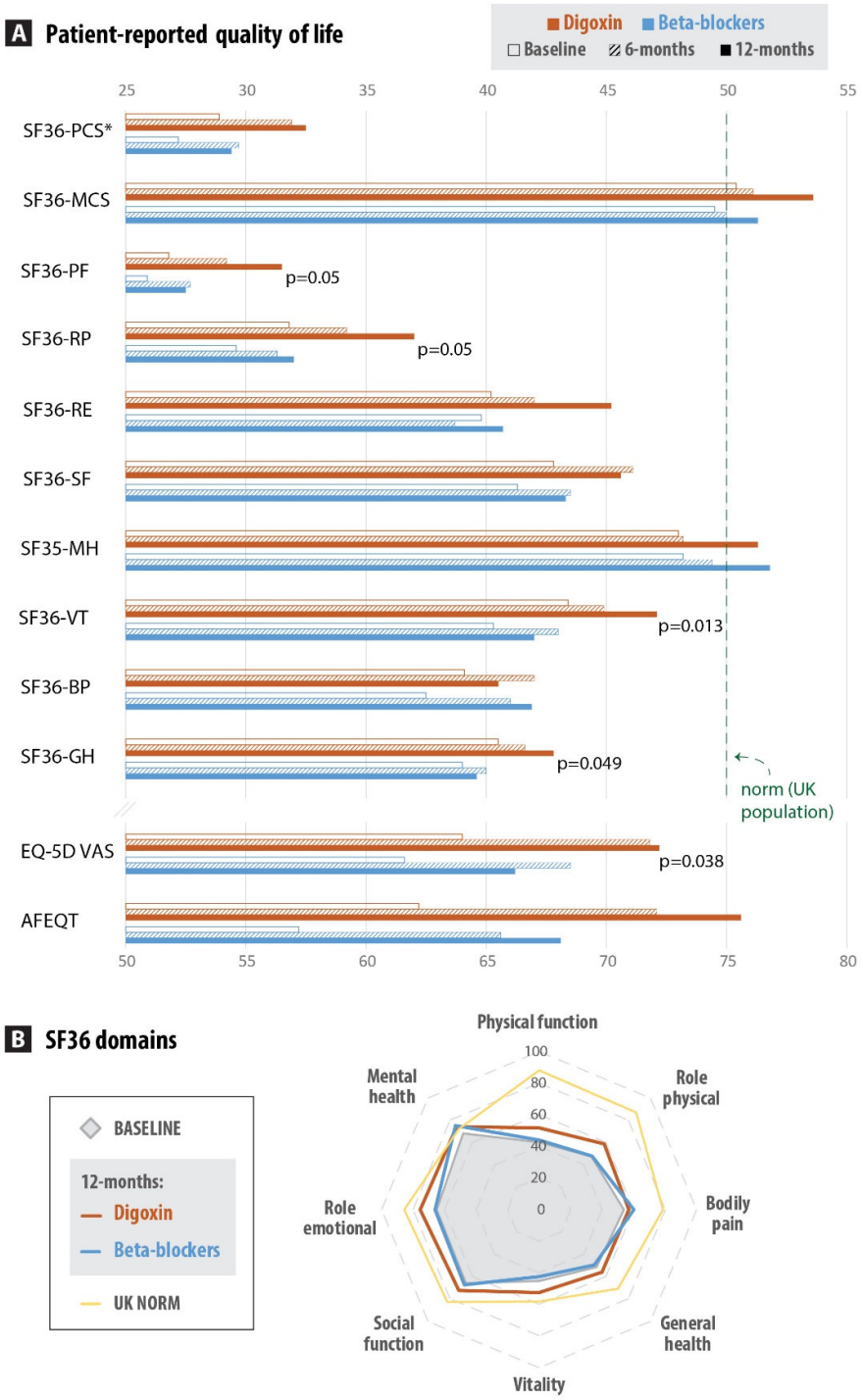
Mean and 95% confidence intervals for 12-lead ECG heart rate; there were no significant differences between digoxin or beta-blocker arms at any time-point. 24-hour heart rate at the end of uptitration was 79±11 beats/min in the digoxin group and 74±11 beats/min in the beta-blocker group (p=0.020).

eFigure 3. Subgroup analyses for the primary outcome



Prespecified subgroup analyses for the SF36 Physical Component Summary Score at 6-months. All subgroups are based on baseline assessment. The beta-blocker 'yes' subgroup refers to patients who received a beta-blocker within one month of randomization. An additional post-hoc subgroup analysis of baseline heart rate <100 vs ≥100 beats/min was also non-significant (p=0.80).

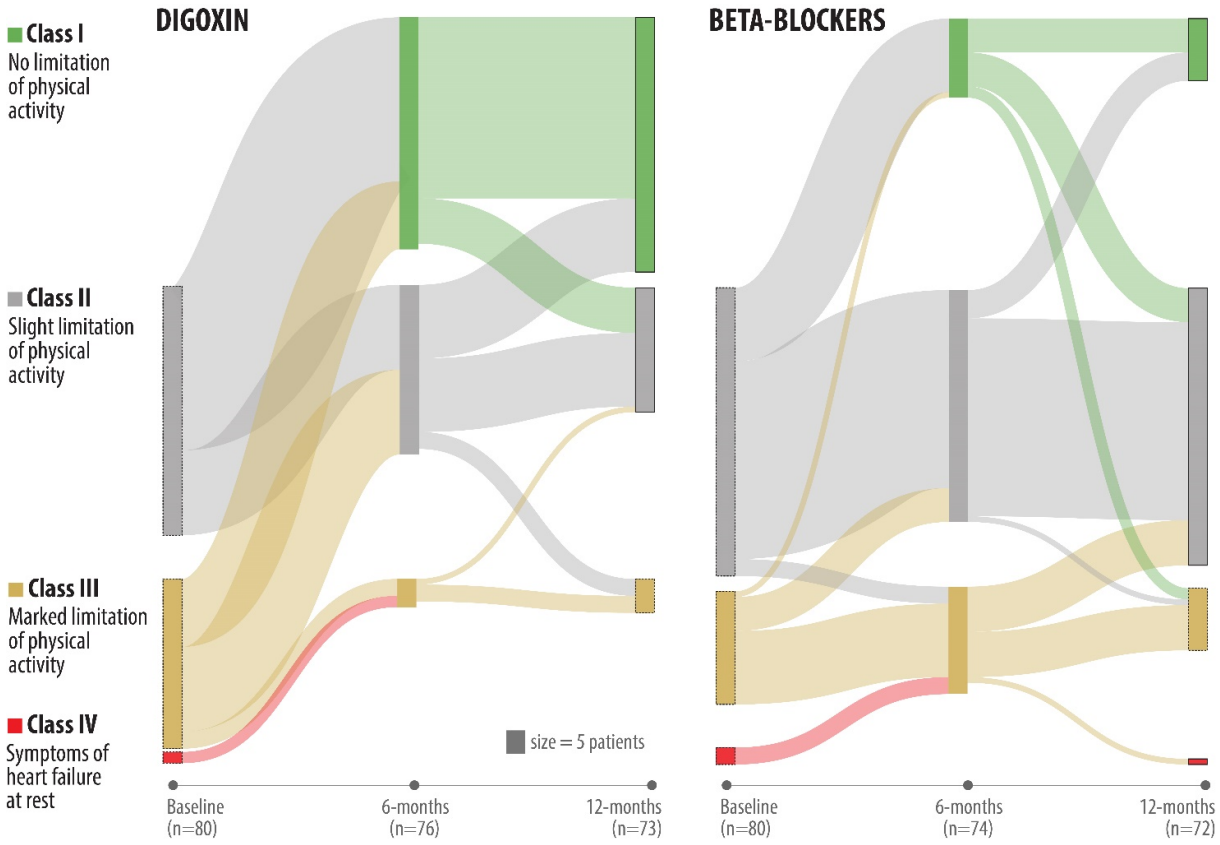
eFigure 4. Change in quality of life



There were no significant differences between digoxin and beta-blocker arms at 6-months; p-values are listed for domains with nominal or significant differences at 12-months. In panel A, SF36 values are normalized to a mean of 50 for the UK population; in panel B, SF36 remain as raw values. UK values are taken from the Third Oxford Health and Lifestyles Survey in primary care (OHLS-III).[6]

SF36 domains are: PCS = physical component summary (* primary outcome); MCS = mental component summary; PF = physical functioning; RP = role physical; RE = role emotional; SF = social functioning; MH = mental health; VT = vitality; BP = bodily pain; GH = global health. EQ-5D VAS = Euroqol 5-dimensions visual analogue score; AFEQT = Atrial Fibrillation Effect on QualiTy-of-life overall score.

eFigure 5. Change in NYHA classification



The NYHA score ranks heart failure-related symptoms and the effect these have on the patient's daily life into four classes, ranging from no limitation (class 1) to inability to carry out any physical activity without discomfort (class 4).

Sankey plots are displayed with bars proportional to the number of patients in each NYHA class at that time-point. There were no patients with a class 1 NYHA score at baseline in either randomized group.

Comparison of NYHA class for digoxin versus beta-blockers using the mean score: Adjusted mean difference at 6-months -0.55, 95% CI -0.73 to -0.38, $p<0.001$; 12-months -0.58, 95% CI -0.76 to -0.39, $p<0.001$; with negative values indicating superiority of digoxin at both time-points.

NYHA = New York Heart Association.

eTable 1. Medication usage over time

Medication details	6-months	12-months
Randomized to DIGOXIN		
Number of patients attended	76	73
Number (%) still receiving digoxin	73 (96.1%)	70 (95.9%)
Digoxin dose, mean micrograms (SD)	160.5 (55.4)	158 (57)
Range of digoxin dose, micrograms	62.5 - 250	62.5 - 250
Digoxin level, mean μg/L (SD)	0.78 (0.31)	0.72 (0.27)
Rate-control drugs used in addition to digoxin	Diltiazem 3 patients (3.9%)	Diltiazem 5 patients (6.8%)
Randomized to BISOPROLOL		
Number of patients attended	74	72
Number (%) still receiving bisoprolol	59 (79.7%)	58 (80.6%)
Dose of bisoprolol, mean milligrams (SD)	3.2 (1.8)	3.3 (2.1)
Range of bisoprolol dose, milligrams	1.0 – 10.0	1.0 – 10.0
Number (%) receiving any beta-blocker	66 (89.2%)	65 (90.3%)
Beta-blockers used other than bisoprolol, agents	Nebivolol 7 patients (9.5%)	Nebivolol 7 patients (9.7%)
Rate-control drugs used in addition to beta-blockers	Diltiazem 1 patient (1.4%)	Diltiazem 1 patient (1.4%)

eTable 2. Resting and exertional heart rate

	Baseline		6-months				12-months			
Resting heart rate										
Heart rate, mean (SD) beats/min	**Digoxin (n=80)**	**Beta-blocker (n=80)**	**Digoxin (n=76)**	**Beta-blocker (n=74)**	**Adjusted mean difference (95% CI)** [a]	**p-value**	**Digoxin (n=73)**	**Beta-blocker (n=72)**	**Adjusted mean difference (95% CI)** [a]	**p-value**
12-lead electrocardiogram	100.3 (16.8)	99.2 (19.2)	76.9 (12.1)	74.8 (11.6)	1.5 (-2.0, 5.1)	0.40	75.4 (9.9)	74.3 (11.2)	0.3 (-3.0, 3.5)	0.87
Apex beat; 30-second measurement	98.3 (15.1)	99.0 (16.8)	78.4 (10.5)	76.2 (11.1)	2.1 (-1.1, 5.3)	0.20	78.3 (9.2)	76.2 (10.6)	1.7 (-1.3, 4.7)	0.26
Radial pulse; 30-second measurement	87.8 (12.0)	86.9 (10.3)	76.2 (9.7)	73.9 (10.8)	1.8 (-1.5, 5.1)	0.29	76.0 (9.0)	73.8 (10.0)	1.5 (-1.7, 4.6)	0.35
Peripheral pulse deficit [b]	-10.3 (9.4)	-12.1 (12.0)	-2.3 (3.9)	-2.3 (4.2)	0.1 (-1.2, 1.5)	0.83	-2.3 (5.1)	-2.3 (3.2)	0.4 (-1.1, 1.8)	0.60
Heart rate at peak of 6-minute walk distance [c]										
Heart rate, mean (SD) beats/min	**Digoxin (n=80)**	**Beta-blocker (n=79)**	**Digoxin (n=74)**	**Beta-blocker (n=73)**	***Adjusted mean difference (95% CI)**	**p-value**	**Digoxin (n=71)**	**Beta-blocker (n=69)**	***Adjusted mean difference (95% CI)**	**p-value**
Radial pulse; 30-second measurement post-exertion [d]	99.9 (19.6)	103.7 (20.2)	90.5 (19.1)	89.8 (18.2)	1.2 (-5.0, 7.5)	0.70	90.1 (15.9)	87.3 (15.2)	2.2 (-3.3, 7.7)	0.43
Difference between exertion and resting heart rate [e]	12.1 (17.8)	16.8 (20.7)	14.3 (19.6)	15.8 (16.4)	-0.8 (-7.0, 5.3)	0.79	13.9 (13.8)	13.7 (15.4)	0.1 (-5.1, 5.4)	0.96

[a] All adjusted models include the baseline score, gender, age at randomization, and baseline mEHRA class and LVEF; differences are in reference to beta-blockers, hence higher values represent better quality of life in the digoxin arm. [b] Difference between radial and apex resting pulse; post-hoc analysis. [c] Some patients were unable to undergo the 6-minute walk due to mobility issues. [d] See Table 3 for walk distance achieved; note the 6-minute walk test is not designed to achieve maximal exertion. [e] Comparing the exertion heart rate with the resting heart rate using the radial pulse; post-hoc analysis.

eTable 3. Generic quality of life data

QoL tool and domain	Baseline		6-months				12-months			
	Digoxin mean (SD)	Beta-blocker mean (SD)	Digoxin mean (SD)	Beta-blocker mean (SD)	Adjusted mean difference (95% CI) [a]	p-value	Digoxin mean (SD)	Beta-blocker mean (SD)	*Adjusted mean difference (95% CI) [a]	p-value
SF36 (normalized for the UK population to a score of 50)										
Physical component summary	28.9 (11.6)	27.2 (10.2)	31.9 (11.7)	29.7 (11.4)	1.4 (-1.1, 3.8)	0.28	32.5 (13.0)	29.4 (12.4)	1.6 (-1.4, 4.7)	0.29
Mental component summary	50.4 (10.2)	49.5 (10.0)	51.1 (10.6)	50.0 (10.4)	0. 7 (-2.4, 3.8)	0.67	53.6 (8.9)	51.3 (10.1)	1.4 (-1.5, 4.2)	0.34
Physical functioning	26.8 (12.6)	25.9 (12.2)	29.2 (13.7)	27.7 (13.6)	1.3 (-1.4, 4.0)	0.36	31.5 (14.1)	27.5 (13.0)	2.8 (0.0, 5.7)	0.05
Role physical	31.8 (12.6)	29.6 (12.1)	34.2 (12.0)	31.3 (12.8)	2.5 (-0.8, 5.8)	0.14	37.0 (12.6)	32.0 (12.4)	3.4 (0.0, 6.9)	0.05
Bodily pain	39.1 (12.2)	37.5 (10.9)	42.0 (12.1)	41.0 (11.6)	0.2 (-3.0, 3.3)	0.92	40.5 (12.7)	41.9 (12.5)	-2.6 (-6.2, 1.1)	0.16
Global health	40.5 (9.4)	39.0 (9.4)	41.6 (9.6)	40.0 (9.8)	1.3 (-1.2, 3.8)	0.30	42.8 (9.9)	39.6 (10.0)	2.8 (0.0, 5.6)	0.05
Vitality	43.4 (9.6)	40.3 (10.0)	44.9 (10.4)	43.0 (10.0)	0.8 (-2.2, 3.7)	0.61	47.1 (9.9)	42.0 (10.0)	3.9 (0.8, 7.0)	0.01
Social function	42.8 (12.3)	41.3 (12.0)	46.1 (11.5)	43.5 (12.5)	2.0 (-1.3, 5.3)	0.23	45.6 (12.3)	43.3 (11.6)	0.9 (-2.7, 4.5)	0.62
Role emotional	40.2 (14.3)	39.8 (15.0)	42.0 (13.3)	38.7 (14.9)	2.9 (-1.2, 7.0)	0.16	45.2 (12.9)	40.7 (15.5)	3.7 (-0.6, 8.1)	0.09
Mental health	48.0 (11.6)	48.2 (9.5)	48.2 (10.7)	49.4 (11.2)	-1.1 (-4.2, 2.1)	0.50	51.3 (9.3)	51.8 (9.5)	-1.0 (-3.6, 1.7)	0.47
EQ-5D-5L										
Index summary	0.67 (0.19)	0.63 (0.22)	0.66 (0.27)	0.65 (0.23)	-0.01 (-0.08, 0.06)	0.80	0.66 (0.27)	0.62 (0.29)	0.01 (-0.06, 0.09)	0.72
Visual analogue scale	64.0 (16.6)	61.6 (20.3)	71.8 (16.3)	68.5 (17.1)	3.6 (-1.3, 8.5)	0.15	72.2 (17.0)	66.2 (17.9)	5.5 (0.3, 10.6)	0.04

[a] All adjusted models include the baseline score, gender, age at randomization, and baseline mEHRA class and LVEF; differences are in reference to beta-blockers, hence higher values represent better quality of life in the digoxin arm.

EQ-5D-5L = Euroqol 5-dimensions 5-levels; QoL = Quality of life; SF36 = Short Form 36-question health survey version 2.

eTable 4. AF-specific quality of life data

QoL tool and domain	Baseline		6-months				12-months			
	Digoxin mean (SD)	Beta-blocker mean (SD)	Digoxin mean (SD)	Beta-blocker mean (SD)	Adjusted mean difference (95% CI) [a]	p-value	Digoxin mean (SD)	Beta-blocker mean (SD)	Adjusted mean difference (95% CI) [a]	p-value
AFEQT										
Overall score	62.2 (16.7)	57.2 (17.6)	72.1 (17.9)	65.6 (16.8)	3.5 (-1.0, 7.9)	0.13	75.6 (17.1)	68.1 (16.1)	4.1 (-0.5, 8.7)	0.08
Symptoms subscale [b]	82.3 (18.3)	76.0 (23.7)	87.2 (14.1)	83.2 (16.4)	2.4 (-2.0, 6.8)	0.29	89.8 (15.5)	86.2 (16.2)	1.0 (-3.7, 5.7)	0.67
Daily activities subscale [b]	44.2 (22.4)	39.3 (22.4)	58.9 (26.0)	47.9 (24.0)	7.1 (0.9, 13.3)	0.025	62.0 (25.1)	48.2 (24.4)	9.4 (2.9, 15.9)	0.005
Treatment concern subscale [b]	72.8 (21.3)	68.4 (21.4)	79.6 (19.4)	77.4 (16.3)	1.1 (-4.6, 6.7)	0.71	84.3 (17.2)	82.5 (14.8)	-0.2 (-5.3, 5.0)	0.95
Treatment satisfaction subscale [b]	55.1 (20.2)	55.3 (21.2)	79.8 (15.0)	73.3 (19.0)	7.0 (1.4, 12.7)	0.015	84.1 (14.0)	75.2 (18.8)	8.8 (3.3, 14.3)	0.002

[a] All adjusted models include the baseline score, gender, age at randomization, and baseline mEHRA class and LVEF; differences are in reference to beta-blockers, hence higher values represent better quality of life in the digoxin arm. [b] Post-hoc analysis.

AFEQT = Atrial Fibrillation Effect on QualiTy-of-life.

eTable 5. Adverse event reporting over 12-months

Adverse event type	Digoxin		Beta-blocker		Total	
	n (%) of patients	**n events**	**n (%) of patients**	**n events**	**n (%) of patients**	**n events**
Gastrointestinal upset	5 (6%)	5	8 (10%)	8	13 (8%)	13
Blurred vision	2 (2%)	2	1 (1%)	1	3 (2%)	3
Rash	1 (1%)	1	0 (0%)	0	1 (1%)	1
Peripheral edema	1 (1%)	1	11 (14%)	12	12 (7%)	13
Symptomatic bradycardia	0 (0%)	0	5 (6%)	5	5 (3%)	5
Dizziness	4 (5%)	4	24 (30%)	28	28 (17%)	32
Headache	5 (6%)	5	9 (11%)	11	14 (9%)	16
Lethargy	7 (9%)	7	30 (38%)	37	37 (23%)	44
Upper respiratory tract symptoms	1 (1%)	1	13 (16%)	15	14 (9%)	16
Symptomatic hypotension	0 (0%)	0	6 (8%)	7	6 (4%)	7
Other	3 (4%)	3	15 (19%)	18	18 (11%)	21
Total events	**-**	**29**	**-**	**142**	**-**	**171**
Number of patients with at least one adverse event [a]	**20 (25%)**		**51 (64%)**		**71 (44%)**	

[a] Chi^2 test for difference in number of patients with at least one adverse event between treatment groups; $p<0.001$.

eTable 6. Studies utilizing the SF36 survey in patients with AF

Study	Instrument	Comment	Clinically important change
Jenkins 2005[17]	SF36 physical functioning	N=716; AF patients randomized to rate or rhythm control	Changes of up to 8 points did not lead to any significant difference in perceived health
Singh 2005[18]	SF36 physical functioning	N=665; Difference in means for AF vs sinus rhythm	Change of 4.8 correlated with improvement in symptom severity and functional capacity[19]
Carlsson 2003[20]	SF36 physical functioning	N=200; AF patients randomized to rhythm or rate control; Difference in means comparing follow-up to baseline in the rate-control group	Change of 4 points did not correlate with any significant changes in AF-related symptoms
Blomström-Lundqvist 2019[21]	SF36 general health	N=155; AF patients randomized to catheter ablation or anti-arrhythmic drugs	A difference in groups of 8.9 equated to a 0.5 class improvement in modified European Heart Rhythm Association score
Grönefeld 2003[22]	SF36 physical component summary	N=102; Patients randomized to the rate control group of a rate vs rhythm control trial	Change of 3.8 equated to an additional 18% of patients reporting they felt much better and 25% somewhat better when asked about any change in their health status since baseline
Erdogan 2003[23]	SF36 physical functioning	N=30; Patients with paroxysmal AF undergoing catheter ablation	Change of 12 was associated with a significant improvement in AF-related symptoms

AF = atrial fibrillation; SF36 = Short Form 36-question health survey version 2.

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