Effect of digoxin vs bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life

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Title: Effect of digoxin vs bisoprolol for rate control in atrial fibrillation on patient-reported quality of life: the RATE-AF randomized clinical trial

Brief Title: Kotecha *et al*, Digoxin vs beta-blockers in permanent atrial fibrillation

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Key points

Question: Is there a difference in patient-reported quality of life among patients with permanent atrial fibrillation, defined as no plans to restore sinus rhythm, and symptoms of heart failure treated with digoxin or beta-blockers for rate control?

Findings:

This clinical trial included 160 adults aged 60 years or greater with atrial fibrillation and symptoms of heart failure, randomized to digoxin (mean attained dose 161mcg) vs bisoprolol (3.2mg). After 6 months, mean SF-36 physical component summary scores (higher better) were 31.5 vs 29.3, respectively, a difference that was not statistically significant.

Meaning: There was no statistically significant difference in patient-reported quality of life; the findings support basing decisions about treatment on other endpoints.

Abstract

Importance: There is little evidence to support selection of rate-control therapy in the growing population with permanent atrial fibrillation (AF), in particular those with coexisting heart failure.

Objective: To compare low-dose digoxin with beta-blockers.

Design, Setting, and Participants: Randomized, open-label, blinded end-point trial of 160 patients aged ≥60 years with permanent AF, defined as no plans to restore sinus rhythm, and at least NYHA class II dyspnea; recruitment from 3 hospitals and primary care in England 2016-2018, with last follow-up October 2019.

Interventions: 1:1 randomization to digoxin (n=80; 62.5-250mcg daily; mean 161mcg) or bisoprolol (n=80; 1.25-15mg daily; mean 3.2mg).

Main Outcomes and Measures: The primary endpoint was patient-reported quality of life using the SF36 Physical Component Summary (PCS) at 6-months (higher better; range 0-100), with a minimal clinically-important difference of 0.5 SD. There were 17 and 20 secondary endpoints at 6 and 12-months respectively, including other QoL outcomes, heart rate, modified European Heart Rhythm Association (mEHRA) symptom classification and NTpro-B-type natriuretic peptide (BNP); in addition to adverse event reporting.

Results: Among 160 patients (mean age, 75.6 years; 74 (46%) women; mean baseline heart rate, 100 [18] beats/min), 145 (91%) completed the trial and 150 (94%) ~~completed~~ were included in the analysis for the primary ~~endpoint~~outcome. ~~Baseline heart rate was 100±18 beats/min, with no significant difference between groups at any time-point.~~ There was no significant difference in the primary outcome: normalized SF36-PCS at 6-months 31.9±11.7 for digoxin and 29.7±11.4 for beta-blockers; adjusted mean difference 1.4, -1.1 to 3.8; p=0.28. Of the 17 secondary outcomes at 6 months, there were no significant between-group differences for 16 outcomes, including resting heart rate (76.9 [12.1] with digoxin vs 74.8 [11.6] with bisoprolol; difference 1.5 beats/min, 95% CI -2.0 to 5.1; p=0.40). ~~Of the 17 secondary comparisons at 6-months, only~~ mEHRA class was

significantly different between groups, with 53% reporting a two-class improvement with digoxin, versus 9% for beta-blockers (adjusted OR 10.3, 4.0-26.6; p<0.001). By 12-months, 8 of 20 outcomes were significantly different (all favoring digoxin), with median NTproBNP 960 pg/mL (626-1531) with digoxin and 1250 pg/mL (847-1890) with beta-blockers; ratio 0.77, 0.64-0.92; p=0.005. Twelve outcomes were not significantly different between groups, including resting heart rate (75.4 [9.9] with digoxin vs 74.3 [11.2] with bisoprolol; difference, 0.3 beats/min, 95% CI -3.0 to 3.5; p=0.87).~~By 12-months, 8/20 outcomes were significantly different (all favoring digoxin) and 12 null. Median NTproBNP was 960 pg/mL in the digoxin group (626-1531) and 1250 pg/mL for beta-blockers (847-1890); ratio 0.77, 0.64-0.92; p=0.005.~~ Adverse events were less common with digoxin, with 20 patients (25%) having at least one event versus 51 (64%) for beta-blockers (p<0.001). The total number of adverse and serious adverse events was 29 and 16 for digoxin, versus 142 and 37 for beta-blockers.

Conclusion and relevance: Among patients aged 60 and older with permanent atrial fibrillation and symptoms of heart failure treated with low-dose digoxin or bisoprolol, there was no statistically significant difference in quality of life at 6 months. These findings support basing decisions about treatment on other endpoints.

Trial registration: clinicaltrials.gov NCT02391337; ISRCTN 95259705; EudraCT 2015-005043-13.

Introduction

Atrial fibrillation (AF) poses a major challenge to healthcare delivery, with high cost and rapidly increasing prevalence in an ageing multi-morbid population.[1] Patients with permanent AF, for whom physicians do not pursue attempts at rhythm control, accounted for 50% of patients with AF in a 2010 global registry.[2] Yet there is almost no robust evidence to support clinical decision-making.[3] Guidance is particularly needed on heart rate control in patients with AF and heart failure, as inappropriate heart rate may worsen heart failure[4,5] and the combination of these conditions increases the risk of hospital admission and mortality.[6,7]

Rate-control in patients with AF and suspected or diagnosed heart failure is usually limited to beta-blockers, digoxin or their combination.[8] Beta-blockers are most widely used due to experience in other cardiovascular conditions[9], and in particular, heart failure with reduced ejection fraction (HFrEF) where in sinus rhythm they improve prognosis regardless of age or gender.[10] However, this finding was not replicated in the subgroup of patients with AF.[7] Digoxin is usually a second-line option, due to neutral mortality effects in randomized clinical trials (RCTs) of HFrEF with sinus rhythm.[11] Although there have been safety concerns from observational studies, digoxin is more commonly used in patients who have a greater comorbidity burden, require additional therapy or are unable to tolerate beta-blockers; all factors associated with a higher risk of adverse events.[12]

The RAte control Therapy Evaluation in permanent Atrial Fibrillation (RATE-AF) trial was designed to compare patient-reported quality of life among patients with permanent atrial fibrillation and symptoms of heart failure treated with low-dose digoxin or beta-blockers for rate control.

Methods

This study was a randomized, open-label, blinded end-point trial comparing heart rate control using low-dose digoxin or beta-blockers. Without any prior comparative evidence, and apparent equipoise for clinical endpoints[7,12], a two-sided hypothesis was adopted. The rationale of the study has been described, with the design informed by a Patient and Public Involvement (PPI) Team[3]; protocol (**Supplement 1**). Ethical approval was obtained from the East Midlands-Derby Research Ethics Committee (16/EM/0178), the Health Research Authority (IRAS 191437) and the Medicines and Healthcare products Regulatory Agency. All participants provided written informed consent after review of the participant information leaflet.

Study participants

Inclusion criteria were: (1) adult patients aged 60 years or older; (2) permanent AF in need of rate-control from a clinician's perspective; (3) breathlessness (equivalent to New York Heart Association Class II or more); and (4) able to provide written informed consent. Permanent AF was defined as a clinical decision for rate control with no plans for cardioversion, anti-arrhythmic drugs or ablation.[8] Exclusion criteria were an established indication for beta-blockers such as myocardial infarction in the last 6 months, contraindications for beta-blockers or digoxin, baseline heart rate <60 beats/min, 2nd/3rd degree heart block, other arrhythmias, pacemaker dependency or planned implantation, obstructive hypertrophic cardiomyopathy or myo/pericarditis, received or planned heart transplant, major surgery within 3 months, and any non-cardiovascular disease expected to reduce life expectancy (**Supplement 3, eFigure 1**). There were no exclusion criteria related to known heart failure or according to left-ventricular ejection fraction (LVEF), apart from those with decompensated heart failure in the last 14 days. Kidney dysfunction was also not an exclusion criterion, as both digoxin and beta-blockers can be safely used with appropriate care and monitoring[13,14]; however, patients receiving renal replacement therapy were excluded due to a lack

of safety information. Participants were asked to self-declare their ethnicity based on the code list for the UK 2011 Census; collection of ethnicity data is used to monitor for health inequalities in the UK National Health Service although individuals are able to decline.

Randomization and masking

After written informed consent, participants were randomized in a 1:1 ratio to either digoxin therapy or bisoprolol via telephone or a web-based portal using a computer-generated minimization algorithm to ensure balance between the treatment groups for baseline modified European Heart Rhythm Association (mEHRA) class and gender. Baseline assessment immediately followed, with allocation concealed until complete; thereafter the trial was open-label. Alternative beta-blockers were acceptable for those with intolerance to bisoprolol. Patients in both groups were given appropriate education about AF and its treatments, in addition to information about the European Society of Cardiology smartphone and tablet application specifically designed for patients with AF (www.escardio.org/af-apps).[15]

Outcomes

The primary endpoint was patient-reported QoL using the SF36 version 2 Physical Component Summary (PCS) score at 6 months' post-randomization. SF36 is a generic QoL questionnaire, chosen due to concerns about the measurement properties of AF-specific tools.[16] Higher scores reflect better QoL, with a scale range of 0-100 for each domain and summary score. As outcomes for patients with both AF and heart failure resemble ~~the~~ those with heart failure~~latter~~[6], the relevant minimal clinically important difference (MCID) for SF36-PCS is between 4.1 and 9.2 (~~patients with heart failure;~~ anchored to mortality).[17] Further detail on outcome derivation and MCIDs for patients with AF are presented in **Supplement 3, eMethods**. Investigators were blinded to SF36, with scoring only performed after the trial was completed.

Secondary endpoints that were investigator-blinded at 6 and 12-months were other SF36 domains, the EuroQol EQ-5D-5L Summary Index Score (0=death to 1=complete health; MCID 0.18), the Atrial Fibrillation Effect on QualiTy-of-life questionnaire (AFEQT; scale ranges 0-100, higher better; MCID 5 points), and NTpro B-type natriuretic peptide (BNP). At 12-months, blinded re-evaluation of cardiac function was performed by a core echocardiography laboratory.[18] Secondary outcomes not investigator-blinded were the EQ-5D-5L Visual Analogue Score (range 0-100, higher better), symptoms and functional capacity assessed using the mEHRA and New York Heart Association (NYHA) class, 6-minute walk distance (6MWD), heart rate and 24-hour ambulatory ECG.

The trial was also designed to collect clinical outcomes to assess safety and plan a larger trial; adverse event collection at each visit included asking patients if they had experienced common adverse events listed in the Summary of Product Characteristics for each drug, and review of the medical record. All serious adverse events and incident cardiovascular events underwent a process of independent adjudication.

Sample size

The primary outcome of SF36-PCS was chosen following review of outcomes relevant to patients by the PPI team, with full rationale presented in the design paper and population values estimated from previous AF trials.[3] The trial was powered to detect an effect size of 0.5 standard deviation (SD) in SF36-PCS. This distributional approach was used as MCID varies across different disease populations and this trial includes patients with both AF and heart failure, as well as a considerable burden of comorbidity. In a systematic review, the 0.5 SD criterion was found to consistently match the MCID regardless of the disease under research[19], and this remains the most common distributional criterion used across different studies.[20] With a two-sided alpha of 0.05, randomizing 144 patients would achieve a power of 85%; hence assuming that 10% of patients would not survive

or be lost to follow-up at 6-months, the sample size required was set at 160 patients. One participant was randomized but did not complete baseline assessment or start the allocated treatment; the Trial Steering Committee decided to replace this participant to maintain the original sample size.

Statistical analysis

A statistical analysis plan was generated and finalized in advance of data analysis (**Supplement 2**). Summary results are presented as percentages, mean and standard deviation (SD), or median and interquartile range (IQR). The full analysis set consisted of patients randomized and receiving at least one dose of therapy, with groups defined by the randomized therapy regardless of treatment withdrawal or crossover. Intervention effects were assessed with the beta-blocker group used as the reference category. All model-based analyses were adjusted for the baseline score (where applicable), minimization parameters (gender and baseline mEHRA), as well as age at randomization and baseline LVEF (as continuous variables). For continuous outcomes, we present the adjusted mean difference (AMD), or in the case of NTproBNP and 6MWD, the ratio of geometric means following log-transformation. For binary and categorical outcomes, logistic and ordinal logistic regression models were used. Count data for events were compared with the Chi-squared test. The change in mEHRA score was compared in an ordinal fashion due to the five categories; in addition the statistical analysis plan pre-specified a comparison of patients who received at least a two-class improvement during follow-up. Pre-specified subgroup analyses for the primary outcome assessed gender, mEHRA class 1/2a versus 2b/3/4, receipt of beta-blockers within the last month prior to randomization, age <75 versus ≥75 years, and LVEF <50 versus ≥50%.

All statistical models were assessed for goodness of fit and interactions, and to ensure there were no violations of any model assumptions. We checked the normality assumption for continuous

outcomes; where this was not met, data were log-transformed prior to analysis. Due to the very limited amount of missing data across all variables and outcomes, complete case data were used for analysis with no imputation performed. ~~Post-hoc analyses are specified in **Supplement 3, eMethods**.~~ The following post-hoc tests were performed: (1) Estimation of the incidence rate ratio for adverse events (zero-inflated negative binomial model) and count data for primary care visits (negative binomial model), with time used as an offset in all models; (2) AFEQT subscales for symptoms, daily activities, treatment concern and treatment satisfaction; (3) Difference between groups in NYHA class; (4) Difference between groups in heart rate deficits; and (5) Additional subgroup analysis for the primary outcome relating to baseline heart rate. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. Statistical analyses were performed on Stata version 16 (StataCorp LP, Texas) and SAS version 9.4 (SAS Institute, North Carolina). A two-tailed p-value of 0.05 was considered a statistically significant difference.

Results

One hundred and 60 patients completed randomization and received at least one dose of allocated treatment, with 80 in each group (**Figure 1**). The mean age was 76 years (SD 8), 46% were women and 7% self-declared non-white ethnicity. The majority of patients at baseline had either moderate troubling symptoms without effect on daily activity (mEHRA class 2b; 47%), or severe symptoms that did impair daily activity (mEHRA class 3; 40%). Mean NYHA class was 2.4 (SD 0.6), with 52% having signs of heart failure on clinical examination. Median NTpro-BNP was 1057 pg/mL (IQR 744-1522) and 19% of patients had LVEF <50% on echocardiography. Groups were well balanced at baseline (**Table 1**), with the exception of more signs of heart failure in those randomized to digoxin. Mean heart rate on the baseline 12-lead ECG was 100 beats/min (SD 18) and was not different between groups. Apart from one patient with an absolute contraindication, all other patients were receiving oral anticoagulants by the end of uptitration.

At 6-months, 73 out of 76 patients (96%) randomized to digoxin were still taking the drug, with a mean dose of 161 mcg (SD 55) and digoxin level of 0.78 ng/mL (SD 0.31). In the beta-blocker group, 66 of 74 patients (89%) were still taking beta-blockers at six months, comprising of 59 still receiving bisoprolol (80%) with a mean dose of 3.2 mg, and 7 (9%) who had switched to alternative beta-blockers due to adverse events. Use of study drugs was similar at 12-months (**Supplement 3, eTable 1**). Over the course of the trial, 5 patients (6.8%) required an additional rate control drug in the digoxin group, compared to 1 patient (1.4%) randomized to beta-blockers. At 12-months, 7 patients (4.8%) were found to be in sinus rhythm (2 digoxin, 5 beta-blockers), 3 had withdrawn and 1 could not attend follow-up (**Figure 1**), with vital status known for all patients. Heart rate responded similarly in both groups over time (**Supplement 3, eFigure 2**). A higher 24-hour heart rate in the digoxin group was noted following uptitration at a mean of 3.1 (SD 2.0) months (AMD 4.3 beats/min, 95% CI 0.7-7.9; p=0.02). There was no significant difference in resting heart rate at

either 6-months (76.9±12.1 versus 74.8±11.6; AMD 1.5 beats/min, 95% CI -2.0 to 5.1; p=0.40) or 12-months (75.4±9.9 versus 74.3±11.2; AMD 0.3 beats/min, 95% CI -3.0 to 3.5; p=0.87), and no significant difference in exercise heart rate at these time points (**Supplement 3, eTable 2**).

Primary endpoint

After 6 months, the mean ~~normalized~~ SF36-PCS normalized for the UK population was 31.9±11.7 for digoxin and 29.7±11.4 for beta-blockers; **Table 2**. There was no significant difference between groups (AMD 1.4, 95% CI -1.1 to 3.8; p=0.28), and no significant findings in subgroup analysis (**Supplement 3, eFigure 3**).

Secondary endpoints

Quality of life: At baseline, QoL was substantially lower than the norm for the UK population in SF36 domains related to physical or functional assessment (**Supplement 3, eFigure 4**). There were no significant differences between digoxin and beta-blockers for SF36 domains at 6-months (**Table 3** and **Supplement 3, eTable 3**). At 12-months, patients randomized to digoxin had significantly better normalized SF36 scores for Vitality (AMD 3.9, 0.8-7.0; p=0.01), General Health (AMD 2.8, 0.0 to 5.6; p=0.05), Physical Functioning (AMD 2.8, 0.0-5.7; p=0.05) and Role-Physical (AMD 3.4, 0.0-6.9; p=0.05) compared to beta-blockers. There was no statistically significant difference in other domains or summaries, including the SF36-PCS (AMD 1.6, -1.4 to 4.7; p=0.29). The EQ-5D-5L visual analogue score was also significantly better in the digoxin group by 12-months (AMD 5.45, 0.30 to 10.61; p=0.04). The AFEQT overall score was not different at either 6 or 12-months.

Symptoms & functional outcomes: The mEHRA functional classification score was substantially better in the digoxin group at follow-up, with 53% of patients reporting a two-class improvement at 6-months, compared to 9% for beta-blockers (adjusted OR 10.3, 4.0 to 26.6; p<0.001). The

significant difference was maintained at 12-months (AMD 5.3, 2.5-11.3; p<0.001), with only 12 patients (16.4%) remaining in class 2b, 3 or 4 in the digoxin group, versus 32 patients (44.4%) in the beta-blocker group (p<0.001; **Figure 2**). Six-minute walk distance in patients randomized to digoxin gradually increased from baseline to 6-months and through to 12-months, an effect which was not seen in the beta-blocker group, although there was no significant difference between groups.

Cardiac function: Median NTproBNP in the digoxin group decreased from 1095 pg/mL (715-1527) to 1057.5 (626-1531) in the first 6-months, then to 960 (626-1531) at 12-months. In contrast, NTproBNP increased in the beta-blocker group from 1041 pg/mL (753-1480) to 1209 (837-1531) at 6-months, and to 1250 (847-1890) at 12-months. There was no significant difference between groups at 6-months (ratio of geometric means 0.85, 0.70-1.03; p=0.09), but statistical significance was reached by 12-months (ratio 0.77, 0.64-0.92; p=0.005; **Table 3**). Mean LVEF increased in both groups, with no statistically significant difference between digoxin and beta-blockers for systolic or diastolic function at 12-months (**Table 3**).

Post-hoc endpoints

The daily activities and treatment satisfaction subscales of AFEQT were significantly better in the digoxin group at both time-points (**Table 3** and **Supplement 3, eTable 4**).

Treatment with digoxin was associated with significantly lower NYHA class at both 6-months (mean 1.5±0.6 versus 2.0±0.6; AMD -0.6, -0.7 to -0.4, p<0.001) and 12-months (mean 1.5±0.6 versus 2.0±0.6; AMD -0.6, -0.8 to -0.4; p<0.001); **Supplement 3, eFigure 5**.

Adverse events

Patients randomized to digoxin had significantly fewer adverse events (**Table 4 and Supplement 3, eTable 5**), with 20 patients (25%) having at least one event versus 51 patients (64%) for beta-

blockers (Chi-squared=24.91; p<0.001). The total number of treatment-related adverse events was 29 in the digoxin group, versus 142 with beta-blockers, with post-hoc incidence rate ratio (IRR) 0.30, 95% CI 0.15 to 0.59; p<0.001. The total number of adjudicated serious adverse events was 16 with digoxin therapy versus 37 with beta-blockers. Three adjudicated cardiovascular events occurred in 2 patients in the digoxin group, compared to 15 events in 12 patients for beta-blockers. Four patients died in those randomized to digoxin (5.0%) and 7 with beta-blockers (8.8%), with one death (1.3%) and four deaths (5.0%) respectively related to cardiovascular causes. There were fewer visits to primary care in the digoxin group related to either AF or another cardiovascular cause. No pacing devices were required in patients randomized to digoxin (0.0%), compared to 3 with beta-blockers (4.2%; of which 2 [2.7%] were for bradycardia indications). Pauses on the 24-hour recording occurred in 33% in those randomized to digoxin (mean duration of the longest pause 2.8±0.4 seconds) and 39% in the beta-blocker group (3.2±1.9 seconds).

Discussion

Among patients aged 60 and older with permanent atrial fibrillation and symptoms of heart failure treated with low-dose digoxin or bisoprolol, there was no statistically significant difference in ~~neither provided superior~~ quality of life results at 6 months. These findings support basing decisions about treatment on other endpoints.

This trial was designed to address a major evidence-gap in the management of patients with AF, with outcomes of concern to patients in this growing population.[21] Heart rate control is often the sole treatment for impaired QoL ~~In~~ in the context of permanent AF, where there has been a joint decision by the patient and physician not to pursue attempts at restoring normal sinus rhythm. ~~heart rate control is often the sole treatment for impaired QoL~~. Without adequate RCTs, clinicians have relied on anecdotal experience to guide rate control therapy, often defaulting to beta-blockers in routine practice. Despite the long history of digoxin[22], non-acute RCTs are only available in the context of heart failure with sinus rhythm.[12] The mechanism of action of digoxin is proposed to include neurohormonal components (anti-adrenergic/pro-vagal), electrophysiological (increased atrioventricular node refractory period), cellular (inhibition of sodium-potassium ATPase), and resultant hemodynamic changes.[13] Beta-adrenergic blockers have been widely studied across different cardiovascular indications, but again there is a lack of data specifically in those with AF.[9] In an individual patient-level meta-analysis of the landmark double-blind HFrEF RCTs, beta-blockers substantially reduced all-cause mortality in sinus rhythm (hazard ratio 0.73; 95% CI 0.67-0.80; p<0·001; n=13,942), but not in the subgroup with AF at baseline (0.97; 95% CI 0.83-1.14; p=0.73; n=3,063).[7] The distinct relationship in AF between heart rate and prognosis may contribute to this difference in efficacy.[23] In the only major RCT comparing heart rate targets in AF, strict heart rate control (predominantly using beta-blockers) did not reduce a composite of clinical events compared to lenient control.[24]

This trial was designed with a two-sided hypothesis for the primary outcome to detect 0.5 SD difference in SF36-PCS. This approach was chosen as 0.5 SD is consistently reflective of the MCID across a range of diseases.[19] MCIDs for SF36 vary according to the methodology involved (criterion, anchor-based or distributional) as well as the disease; in a study of 31,325 Medicare patients with heart failure published by the instrument developers, the MCID for SF36-PCS was 4.1 corresponding to a 20% increased mortality risk, and 9.2 for a 50% increase.[17] In independent studies, MCIDs of 5.5 for SF36-PCS have been suggested for cervical myelopathy[25], for knee arthritis 10[26], rheumatoid arthritis 7.2[27], pulmonary fibrosis 5.0[28] and carotid artery disease 8.2.[29] Although MCID approaches have been criticized[30], these ranges are consistent with clinical correlates seen in rhythm control trials of patients with AF (**Supplement 3, eTable 6**), including a recent study where an 8.9 score difference in SF36 general health had clinical relevance.[31] The upper 95% confidence limit for the primary outcome comparing digoxin with beta-blockers in this trial was 3.9, suggesting that the difference in effect of these drugs on SF36-PCS at 6-months (adjusted for baseline score) is not a clinically-important difference.

Secondary endpoints should be considered as exploratory and hypothesis generating; by 12-months, 8/20 outcomes were significantly different (all favoring digoxin) and 12 null, with better symptom control with digoxin for both AF and heart failure-related symptoms consistent with a significantly lower NTproBNP and adverse events compared to the beta-blocker group. There was no requirement for pacemakers, no increase in pauses and no deterioration in LVEF with digoxin therapy, and in contrast to short-term RCTs, there was no statistically significant difference compared to beta-blockers in longer-term heart rate. Concerns in the use of digoxin, such as the narrow therapeutic window and drug interactions were not an issue in this low-dose approach.

Entry criteria relating to heart failure were avoided due to the difficulties in ascertaining this

diagnosis in AF, both for HFrEF (where there is no data on the validity of measuring systolic function in AF[32]) and also heart failure with preserved LVEF (where symptomatic improvement using diuretics may be required to separate overlapping diagnostic features[5]). The majority of patients in the trial also had other comorbidities, with patient focus groups suggesting that benefit to AF-related symptoms was often offset by enhanced appreciation of these comorbidities (particularly large-joint arthritis) leading to a neutral effect on overall QoL.[21] This may explain why no significant difference between groups was identified for summary QoL domains and 6MWD, which highlights the importance of broad and inclusive management of patients with AF[8] and an integrated management approach.[33]

Limitations

This study has several limitations. First, the trial used an open-label design as a blinded approach was felt to be impractical in the context of the embedded healthcare design, and unethical due to the lack of prior trial data and potential need for additional therapy with intercurrent illness or hospitalization (extremely common in this older comorbid patient group). The trial design maintained the benefits associated with a strict randomization procedure, while the blinded endpoint assessment helped to reduce bias (especially as the primary endpoint was subjective). Second, although there was a considerable and statistically significant difference between groups for the pre-specified comparison of adverse events, this endpoint was secondary and the trial lacked power for comparison of major adverse cardiovascular events, which deserves further study. Third, the findings do not apply to patients with severe reduction in LVEF (where numbers in the trial are limited), or those admitted with uncontrolled AF or decompensated heart failure, as acute heart rate control in these scenarios is often more challenging. With broad inclusion and minimal exclusion criteria, patients in this trial reflect usual clinical practice of those requiring outpatient heart rate control with permanent AF and symptoms of heart failure.

Conclusions

Among patients aged 60 and older with permanent atrial fibrillation and symptoms of heart failure treated with low-dose digoxin or bisoprolol, there was no statistically significant difference in ~~neither provided superior~~ QoL results at 6 months. These findings support basing decisions about treatment on other endpoints.

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Data Sharing Statement

See Supplement 4.

Access to Data

The Chief Investigator, Professor Dipak Kotecha, and Trial Statistician, Samir Mehta, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Role of the Funder/Sponsor

Neither the Sponsor (University of Birmingham) nor the Funder (UK National Institute for Health Research) had any role in the design and conduct of the study; collection, management, analysis,

and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Neither organization had the right to veto publication or to control the decision regarding to which journal the paper was submitted.

Competing interests

All authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare:
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Authors' contributions

The manuscript was drafted by DK who is the Chief Investigator for the RATE-AF trial, with the assistance of the Patient and Public Involvement Team (MS, JJ and SH). KVB and SKG were the research assistants, SM the trial statistician, and MG, JNT and GYHL the Principal Investigators. AJC was the independent chair of the Trial Steering Committee; KR the independent chair of the Data Monitoring Committee, and VYS the independent statistician. All other authors listed were ~~either~~ members of the Trial Management Group ~~or the Oversight Committees~~. All authors contributed to the writing of the RATE-AF protocol, and edited this manuscript for intellectual content.

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579

Table 1: Characteristics at the baseline visit

Characteristic		Digoxin (n=80)	Beta-blocker (n=80)
Demographics & Comorbidities [a]			
Age, mean years (SD)		74.5 (8.3)	76.8 (8.1)
Gender, n women (%)		36 (45.0%)	38 (47.5%)
Gender, n men (%)		44 (55.0%)	42 (52.5%)
~~Ethnicity~~ Heritage [b]	Asian/Asian British	3 (3.8%)	5 (6.3%)
	Black/African/Caribbean/ Black British	2 (2.5%)	1 (1.3%)
	White British/Irish	75 (93.8%)	74 (92.5%)
Treatment for hypertension, n (%)		56 (70.0%)	60 (75.0%)
Airways disease, n (%)		24 (30.0%)	18 (22.5%)
Diabetes mellitus, n (%)		16 (20.0%)	22 (27.5%)
Unplanned admission for either AF or heart failure in the last 12 months, n (%)		16 (20.0%)	15 (18.8%)
Previous stroke or TIA, n (%)		12 (15.0%)	16 (20.0%)
Atrial fibrillation metrics			
Previous use of anti-arrhythmic drugs, n (%)		5 (6.3%)	8 (10.0%)
Previous AF cardioversion, n (%)		6 (7.5%)	9 (11.3%)
Previous AF ablation, n (%)		2 (2.5%)	1 (1.3%)
modified European Heart Rhythm Association class, n (%) [c]	1	0 (0.0%)	0 (0.0%)
	2a	3 (3.8%)	3 (3.8%)
	2b	34 (42.5%)	40 (50.0%)
	3	38 (47.5%)	27 (33.8%)
	4	5 (6.3%)	10 (12.5%)
Heart failure metrics			
Previous diagnosis of heart failure, n (%)		35 (43.8%)	24 (30.0%)
Signs of heart failure at baseline, n (%) [d]		49 (61.3%)	35 (43.8%)
NTproBNP, median pg/mL (1st quartile, 3rd quartile)		1095 (715-1527)	1041 (753-1480)
Echocardiogram LVEF, mean % (SD)		56.2 (8.8)	57.6 (10.5)
Echocardiogram LVEF <50%, n (%)		17 (21.3%)	13 (16.3%)
New York Heat Association class, n (%) [e]	I	0 (0.0%)	0 (0.0%)
	II	46 (57.5%)	53 (66.3%)
	III	32 (40.0%)	24 (30.0%)
	IV	2 (2.5%)	3 (3.8%)
	mean (SD)	2.4 (0.5)	2.4 (0.6)
Current use of ACE inhibitors, ARB or aldosterone antagonists		49 (61.3%)	45 (56.3%)
Current use of thiazide or loop diuretics		23 (28.8%)	26 (32.5%)
Clinical measurements			
12-lead ECG heart rate, mean beats/min (SD)		100.1 (16.8)	99.2 (19.2)

Characteristic	Digoxin (n=80)	Beta-blocker (n=80)
Apex 30-second heart rate, mean beats/min (SD)	98.2 (15.1)	99.0 (16.8)
Radial pulse 30-second heart rate, mean beats/min (SD) [f]	87.8 (12.1)	86.9 (10.3)
Systolic blood pressure, mean mmHg (SD)	134.2 (14.7)	137.1 (17.5)
Creatinine, median (1st quartile, 3rd quartile)	85 µmol/L (71-97) 0.96 mg/dL (0.80-1.10)	87 µmol/L (75-105) 0.98 mg/dL (0.85-1.19)
6-minute walk distance, median meters 1st quartile, 3rd quartile) [g]	321 (120-419)	330 (90-450)

[a] Medical conditions were based on patient reporting and review of the medical record. Note that due to rounding, some categories do not total 100%.

[b] Ethnicity was self-reported and based on United Kingdom census categories.

[c] Modified European Heart Rhythm Association class 1 = No symptoms from AF; 2a = Mild symptoms, normal daily activity not affected and patient not troubled by symptoms; 2b = Moderate symptoms, normal daily activity not affected but patient troubled by symptoms; 3 = Severe symptoms, with normal daily activity affected by symptoms relating to AF; 4 = Disabling symptoms, with normal daily activity discontinued.

[d] Signs consistent with current heart failure as determined by the clinical investigator, including lung crepitations, peripheral edema, raised jugular venous pressure and abnormal heart sounds.

[e] New York Heat Association class I = No limitation of physical activity, with ordinary physical activity not causing undue fatigue, palpitation or dyspnea; II = Slight limitation of physical activity, comfortable at rest, but ordinary physical activity resulting in fatigue, palpitation or dyspnea; III = Marked limitation of physical activity, comfortable at rest, but less than ordinary activity causing fatigue, palpitation or dyspnea; IV = Unable to carry out any physical activity without discomfort, symptoms of heart failure at rest, and if any physical activity is undertaken, discomfort increases.

[f] The radial heart rate was taken immediately before the apex heart rate; this demonstrates the degree of discrepancy between central and peripheral pulse measurement in the context of AF (see Supplement 3, eTable 2).

[g] In healthy individuals in the age range of 70-80 years, the expected median 6-minute walk distance is approximately 500m based on data from 88 persons from a global multicenter study.[34]

AF = atrial fibrillation; BNP = B-type natriuretic peptide; ECG = electrocardiogram; LVEF = left-ventricular ejection fraction; TIA = transient ischemic attack.

Table 2: Primary outcome

	Baseline		6-months			
	Digoxin (n=80)	**Beta-blocker (n=80)**	**Digoxin (n=76)**	**Beta-blocker (n=74)**	**Adjusted mean difference (95% CI) [a]**	**p-value**
Short Form survey 36 (SF36) Physical component summary score [b]	28.5 (12.0)	26.7 (10.5)	31.5 (12.0)	29.3 (11.7)	1.3 (-1.2, 3.9)	0.30
Short Form survey 36 (SF36) Physical component summary score normalized for the UK population [c]	28.9 (11.6)	27.2 (10.2)	31.9 (11.7)	29.7 (11.4)	1.4 (-1.1, 3.8)	0.28

[a] The adjusted mean difference is the difference in SF36-PCS at 6-months comparing digoxin with beta-blockers adjusted for baseline values; for example in the top row 31.5 v 29.3 and not the difference in change from baseline (in this case 3.0 v 2.6). The beta-blocker group is used as the reference, so higher values indicate better response with digoxin therapy. All adjusted models also include gender, age at randomization, modified European Heart Rhythm Association class and left-ventricular ejection fraction.

[b] The Short Form survey 36 (SF36) is generated by patient responses to 36 questions reflecting 8 domains of general physical and emotional health. The Physical Component Summary (PCS) ranges from 0 to 100, with higher values indicating better patient-reported quality of life. See Supplement 3, eMethods for scoring process.

[c] Allows for comparison across studies, with a score of 50 being the expected normal score. See Supplement 3, eFigure 3 for the component domains.

Table 3: Secondary outcomes at 12-months

Outcome	Baseline		12-months			
	Digoxin (n=80)	Beta-blocker (n=80)	Digoxin (n=73)	Beta-blocker (n=72)	Adjusted mean difference [a]	p-value
Heart rate, mean (SD) beats/min						
12-lead electrocardiogram	100.3 (16.8)	99.2 (19.2)	75.4 (9.9)	74.3 (11.2)	0.3 (-3.0, 3.5)	0.87
Patient-reported quality of life [b], mean (SD)						
SF36 Physical component summary	28.9 (11.6)	27.2 (10.2)	32.5 (13) [c]	29.4 (12.4)	1.6 (-1.4, 4.7)	0.29
SF36 Physical functioning	26.8 (12.6)	25.9 (12.2)	31.5 (14.1)	27.5 (13.0)	2.8 (0.0, 5.7)	0.05
SF36 Role physical	31.8 (12.6)	29.6 (12.1)	37.0 (12.6)	32.0 (12.4)	3.4 (0.0, 6.9)	0.05
SF36 Vitality	43.4 (9.6)	40.3 (10.0)	47.1 (9.9)	42.0 (10.0)	3.9 (0.8, 7.0)	0.01
SF36 Global health	40.5 (9.4)	39 (9.4)	42.8 (9.9) [c]	39.6 (10.0)	2.8 (0.0, 5.6)	0.05
EQ-5D-5L Summary index score	0.67 (0.19)	0.63 (0.22)	0.66 (0.27)	0.62 (0.29)	0.01 (-0.06, 0.09)	0.72
EQ-5D-5L Visual analogue scale	64.0 (16.6)	61.6 (20.3)	72.2 (17.0)	66.2 (17.9)	5.5 (0.3, 10.6)	0.04
AFEQT overall score	62.2 (16.7)	57.2 (17.6)	75.6 (17.1)	68.1 (16.1)	4.1 (-0.5, 8.7)	0.08
AFEQT daily activities subscale [d]	44.2 (22.4)	39.3 (22.4)	62.0 (25.1)	48.2 (24.4)	9.4 (2.9, 15.9)	0.005
AFEQT treatment satisfaction subscale [d]	55.1 (20.2)	55.3 (21.2)	84.1 (14.0)	75.2 (18.8)	8.8 (3.3, 14.3)	0.002
Functional outcomes						
mEHRA, n (%) two-class improvement from baseline	-	-	50 (68.5%)	21 (29.2%)	5.3 (2.5, 11.3) [e]	<0.001
NYHA class, mean (SD) [d]	2.4 (0.5)	2.4 (0.6)	1.5 (0.6)	2.0 (0.6)	-0.6 (-0.8, -0.4)	<0.001
6-minute walk distance, median meters (SD) [f]	321 (120-419)	330 (90-450)	366 (233-435)	329 (120-429)	1.1 (0.9, 1.3) [g]	0.25
Cardiac function						

Outcome	Baseline		12-months			
	Digoxin (n=80)	Beta-blocker (n=80)	Digoxin (n=73)	Beta-blocker (n=72)	Adjusted mean difference [a]	p-value
NTproBNP, median (IQR)	1091 (710-1522)	1041 (753-1480)	960 (626-1531)	1250 (847-1890)	0.77 (0.64, 0.92) [g]	0.005
Left-ventricular ejection fraction, mean % (SD)	56.2 (8.8)	57.6 (10.5)	59.7 (8.7)	59.8 (7.3)	0.8 (-1.3, 3.0)	0.45
Ratio of early mitral inflow to annular early diastolic velocity (E/e'), mean ratio (SD)	10.7 (4.5)	10.2 (4.7)	10.8 (5.1)	10.8 (5.5)	-0.1 (-1.1, 0.9)	0.81
Diastolic dysfunction composite, n (%)	13 (16%)	8 (10%)	8 (11%)	7 (10%)	1.3 (0.3, 4.8) [e]	0.73

A full list of secondary quality of life outcomes at both 6 and 12-months is presented in Supplement 3, eTables 2, 3 and 4. For description of the mEHRA and NYHA classification, see legend for Table 1.

[a] The adjusted mean difference is the difference in outcome at 12-months comparing digoxin with beta-blockers adjusted for baseline values; that is, for heart rate, 75.4 v 74.3 and not the difference in change from baseline (in this case 24.9 v 24.9). The beta-blocker group is used as the reference, so higher values indicate better response with digoxin therapy. All adjusted models include the baseline score, gender, age at randomization, and baseline mEHRA class and left-ventricular ejection fraction.

[b] For all quality of life scales, higher values indicate better patient-reported quality of life. Details on each instrument and the scoring process are presented in the Supplement 3, eMethods. The SF36 and EQ-5D-5L instruments are both generic quality of life tools; SF36 has a recall period of 4 weeks and EQ-5D-5L asks about quality of life on that day. The AFEQT instrument is an AF-specific quality of life tool (recall period 4 weeks) with questions tailored to atrial fibrillation symptoms and treatments. The SF36 values presented are normalized to the UK population (norm = 50), with the low mean values indicative of substantial impairment of QoL in this patient population.

[c] One patient is missing data for this SF36 summary/domain.

[d] Post-hoc analysis.

[e] Adjusted odds ratio.

[f] In healthy individuals in the age range of 70-80 years, the expected median 6-minute walk distance is approximately 500m based on data from 88 persons from a global multicenter study.[34]

[g] Ratio of geometric means due to skewed data.

AFEQT = Atrial Fibrillation Effect on QualiTy-of-life; BNP = B-type natriuretic peptide; EQ-5D-5L = Euroqol 5-dimensions 5-levels; LVEF = left-ventricular ejection fraction; mEHRA = modified European Heart Rhythm Association; NYHA = New York Heart Association; QoL = Quality of life; SF36 = Short Form 36-question health survey version 2.

Table 4: Detail of clinical events through 12 months by randomized group

Outcome	Digoxin (n=80)	Beta-blocker (n=80)
Deaths		
Number (%)	4 (5.0%) [a]	7 (8.8%) [b]
Adjudicated cardiovascular events [c]		
Total number	3 (in 2 patients) [d]	15 (in 12 patients) [e]
Unplanned hospitalizations		
Total number	12 (in 11 patients)	28 (in 19 patients)
Number with two or more hospital admissions	1	9
Serious adverse events [f]		
Total number	16 (in 13 patients)	37 (in 21 patients)
Treatment-related adverse events [g]		
Total number	29	142
Number (%) with at least one event	20 (24.7%)	51 (63.8%)
Primary care visits in addition to study visits [h]		
Total number of visits	192 (in 64 patients)	228 (in 68 patients)
Number of visits due to atrial fibrillation	6 (in 4 patients)	30 (in 21 patients)
Number of visits due to other cardiovascular cause	16 (in 9 patients)	34 (in 23 patients)
Number of visits due to non-cardiovascular or other cause	170 (in 61 patients)	164 (in 58 patients)

[a] Causes of death were ischemic heart disease, bladder cancer, aspiration pneumonia in the context of colon cancer, and liver cirrhosis in the context of alcoholic liver disease.

[b] Causes of death were congestive cardiac failure, decompensated heart failure in the context of severe valve disease, non-Hodgkin's lymphoma, cardio-renal syndrome, myocardial infarction, pancreatic cancer, and perforated bowel secondary to diverticular disease.

[c] For any potential cardiovascular event, an independent clinician reviewed medical records, blood results and imaging, and completed a pre-specified structured case report form that was sent directly to the trials unit.

[d] Primary causes were myocardial infarction, peripheral edema after diuretics were inadvertently paused, and palpitations with no change to management.

[e] Primary causes were pacemaker implantation x 2 (bradycardia and/or pauses), decompensated heart failure x 3, myocardial infarction x 2, troponin-negative chest pain x 2, acute stroke x 2, collapse and bradycardia, heart failure and bradycardia, rapid AF and dyspnea, and endocarditis.

[f] Serious adverse events are any adverse event, adverse reaction or unexpected adverse reaction, respectively, that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect; all such events underwent appraisal by a Principal Investigator within one working day, followed by confirmatory processes by the Chief Investigator.

[g] At each study visit, patients were asked to report any adverse events since the last visit from a list taken from the Summary of Product Characteristics for each drug.

[h] On average, there were 3.2 primary care contacts per patient in addition to trial visits; in a national survey in Scotland, the average number of contacts per patient (with newly diagnosed AF) was between 4.2 and 7.8.[35]

Figure legends

Figure 1: Flowchart of study enrollment and analysis

[a] Randomization was not purely random but with minimization to balance gender and the modified European Heart Rhythm Association class at baseline.

[b] Or another beta-blocker if intolerance to bisoprolol.

[c] One patient completed 35 of 36 elements of the Short Form survey 36 (SF-36) questionnaire at 12 months.

See Table 1 for explanation of New York Heart Association class.

Figure 2: Change in symptom classification

The mEHRA score ranks AF-related symptoms and the effect these have on the patient's daily life into five classes, ranging from asymptomatic (class 1) to disabling (class 4). The modified score subdivides class 2 into 'a' (not troubling) and 'b' (troubling) to identify patients in need of further intervention. Sankey plots are displayed with bars proportional to the number of patients in each mEHRA class at that time-point. There were no patients with a class 1 mEHRA score at baseline in either randomized group. Comparison of mEHRA class using ordinal logistic regression across all categories for digoxin versus beta-blockers: Adjusted odds ratio at 6-months 0.12, 95% CI 0.06-0.25, $p<0.001$; at 12-months 0.16, 95% CI 0.08-0.33, $p<0.001$; with an odds ratio less than 1 indicating superiority of digoxin at both time-points. See **Supplement 3, eFigure 5** for the change in New York Heart Association class during the study.

AF = atrial fibrillation; mEHRA = modified European Heart Rhythm Association.