

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

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1 **Title: Effect of digoxin vs bisoprolol for rate control in atrial**
2 **fibrillation on patient-reported quality of life: the RATE-**
3 **AF randomized clinical trial**
4

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

6
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41 | digoxin; beta-blockers.

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46 | **Key points**

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

51 | **Findings:**

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

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

59 Abstract

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

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

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

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

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

75 **Results:** Among 160 patients (mean age, 75.6 years; 74 (46%) women; mean baseline heart rate,
76 100 [18] beats/min), 145 (91%) completed the trial and 150 (94%) ~~completed~~ were included in the
77 analysis for the primary endpoint outcome. Baseline heart rate was 100 \pm 18 beats/min, with no
78 significant difference between groups at any time point.—There was no significant difference in the
79 primary outcome: normalized SF36-PCS at 6-months 31.9 \pm 11.7 for digoxin and 29.7 \pm 11.4 for beta-
80 blockers; adjusted mean difference 1.4, -1.1 to 3.8; p=0.28. Of the 17 secondary outcomes at 6
81 months, there were no significant between-group differences for 16 outcomes, including resting
82 heart rate (76.9 [12.1] with digoxin vs 74.8 [11.6] with bisoprolol; difference 1.5 beats/min, 95% CI
83 -2.0 to 5.1; p=0.40). Of the 17 secondary comparisons at 6 months, only mEHRA class was

84 significantly different between groups, with 53% reporting a two-class improvement with digoxin,
85 versus 9% for beta-blockers (adjusted OR 10.3, 4.0-26.6; $p < 0.001$). By 12-months, 8 of 20
86 outcomes were significantly different (all favoring digoxin), with median NTproBNP 960 pg/mL
87 (626-1531) with digoxin and 1250 pg/mL (847-1890) with beta-blockers; ratio 0.77, 0.64-0.92;
88 $p = 0.005$. Twelve outcomes were not significantly different between groups, including resting heart
89 rate (75.4 [9.9] with digoxin vs 74.3 [11.2] with bisoprolol; difference, 0.3 beats/min, 95% CI -3.0
90 to 3.5; $p = 0.87$).~~By 12 months, 8/20 outcomes were significantly different (all favoring digoxin) and~~
91 ~~12 null. Median NTproBNP was 960 pg/mL in the digoxin group (626-1531) and 1250 pg/mL for~~
92 ~~beta-blockers (847-1890); ratio 0.77, 0.64-0.92; $p = 0.005$.~~ Adverse events were less common with
93 digoxin, with 20 patients (25%) having at least one event versus 51 (64%) for beta-blockers
94 ($p < 0.001$). The total number of adverse and serious adverse events was 29 and 16 for digoxin,
95 versus 142 and 37 for beta-blockers.

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

100

101 **Trial registration:** [clinicaltrials.gov NCT02391337](https://clinicaltrials.gov/ct2/show/study/NCT02391337); [ISRCTN 95259705](https://www.isrctn.com/ISRCTN95259705); [EudraCT 2015-005043-](https://eudraCT.europa.eu/number/2015-005043-13)
102 [13](https://eudraCT.europa.eu/number/2015-005043-13).

103

104

105 **Introduction**

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

113

114 Rate-control in patients with AF and suspected or diagnosed heart failure is usually limited to beta-
115 blockers, digoxin or their combination.⁸ Beta-blockers are most widely used due to experience in
116 other cardiovascular conditions⁹, and in particular, heart failure with reduced ejection fraction
117 (HFrEF) where in sinus rhythm they improve prognosis regardless of age or gender.¹⁰ However,
118 this finding was not replicated in the subgroup of patients with AF.⁷ Digoxin is usually a second-
119 line option, due to neutral mortality effects in randomized clinical trials (RCTs) of HFrEF with
120 sinus rhythm.¹¹ Although there have been safety concerns from observational studies, digoxin is
121 more commonly used in patients who have a greater comorbidity burden, require additional therapy
122 or are unable to tolerate beta-blockers; all factors associated with a higher risk of adverse events.¹²

123

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

128 **Methods**

129 This study was a randomized, open-label, blinded end-point trial comparing heart rate control using
130 low-dose digoxin or beta-blockers. Without any prior comparative evidence, and apparent
131 equipoise for clinical endpoints^{7,12}, a two-sided hypothesis was adopted. The rationale of the study
132 has been described, with the design informed by a Patient and Public Involvement (PPI) Team³;
133 protocol (**Supplement 1**). Ethical approval was obtained from the East Midlands-Derby Research
134 Ethics Committee (16/EM/0178), the Health Research Authority (IRAS 191437) and the Medicines
135 and Healthcare products Regulatory Agency. All participants provided written informed consent
136 after review of the participant information leaflet.

137

138 **Study participants**

139 Inclusion criteria were: (1) adult patients aged 60 years or older; (2) permanent AF in need of rate-
140 control from a clinician's perspective; (3) breathlessness (equivalent to New York Heart
141 Association Class II or more); and (4) able to provide written informed consent. Permanent AF was
142 defined as a clinical decision for rate control with no plans for cardioversion, anti-arrhythmic drugs
143 or ablation.⁸ Exclusion criteria were an established indication for beta-blockers such as myocardial
144 infarction in the last 6 months, contraindications for beta-blockers or digoxin, baseline heart rate
145 <60 beats/min, 2nd/3rd degree heart block, other arrhythmias, pacemaker dependency or planned
146 implantation, obstructive hypertrophic cardiomyopathy or myo/pericarditis, received or planned
147 heart transplant, major surgery within 3 months, and any non-cardiovascular disease expected to
148 reduce life expectancy (**Supplement 3, eFigure 1**). There were no exclusion criteria related to
149 known heart failure or according to left-ventricular ejection fraction (LVEF), apart from those with
150 decompensated heart failure in the last 14 days. Kidney dysfunction was also not an exclusion
151 criterion, as both digoxin and beta-blockers can be safely used with appropriate care and
152 monitoring^{13,14}; however, patients receiving renal replacement therapy were excluded due to a lack

153 of safety information. Participants were asked to self-declare their ethnicity based on the code list
154 for the UK 2011 Census; [collection of ethnicity data is used to monitor for health inequalities in the](#)
155 [UK National Health Service although individuals are able to decline.](#)
156

157 **Randomization and masking**

158 After written informed consent, participants were randomized in a 1:1 ratio to either digoxin
159 therapy or bisoprolol via telephone or a web-based portal using a computer-generated minimization
160 algorithm to ensure balance between the treatment groups for baseline modified European Heart
161 Rhythm Association (mEHRA) class and gender. Baseline assessment immediately followed, with
162 allocation concealed until complete; thereafter the trial was open-label. Alternative beta-blockers
163 were acceptable for those with intolerance to bisoprolol. Patients in both groups were given
164 appropriate education about AF and its treatments, in addition to information about the European
165 Society of Cardiology smartphone and tablet application specifically designed for patients with AF
166 (www.escardio.org/af-apps).¹⁵
167

168 **Outcomes**

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

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

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

192

193 **Sample size**

194 The primary outcome of SF36-PCS was chosen following review of outcomes relevant to patients
195 by the PPI team, with full rationale presented in the design paper and population values estimated
196 from previous AF trials.³ The trial was powered to detect an effect size of 0.5 standard deviation
197 (SD) in SF36-PCS. This distributional approach was used as MCID varies across different disease
198 populations and this trial includes patients with both AF and heart failure, as well as a considerable
199 burden of comorbidity. In a systematic review, the 0.5 SD criterion was found to consistently
200 match the MCID regardless of the disease under research¹⁹, and this remains the most common
201 distributional criterion used across different studies.²⁰ With a two-sided alpha of 0.05, randomizing
202 144 patients would achieve a power of 85%; hence assuming that 10% of patients would not survive

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

207

208 **Statistical analysis**

209 A statistical analysis plan was generated and finalized in advance of data analysis (**Supplement 2**).

210 Summary results are presented as percentages, mean and standard deviation (SD), or median and
211 interquartile range (IQR). The full analysis set consisted of patients randomized and receiving at
212 least one dose of therapy, with groups defined by the randomized therapy regardless of treatment
213 withdrawal or crossover. Intervention effects were assessed with the beta-blocker group used as the
214 reference category. All model-based analyses were adjusted for the baseline score (where
215 applicable), minimization parameters (gender and baseline mEHRA), as well as age at
216 randomization and baseline LVEF (as continuous variables). For continuous outcomes, we present
217 the adjusted mean difference (AMD), or in the case of NTproBNP and 6MWD, the ratio of
218 geometric means following log-transformation. For binary and categorical outcomes, logistic and
219 ordinal logistic regression models were used. Count data for events were compared with the Chi-
220 squared test. The change in mEHRA score was compared in an ordinal fashion due to the five
221 categories; in addition the statistical analysis plan pre-specified a comparison of patients who
222 received at least a two-class improvement during follow-up. Pre-specified subgroup analyses for
223 the primary outcome assessed gender, mEHRA class 1/2a versus 2b/3/4, receipt of beta-blockers
224 within the last month prior to randomization, age <75 versus ≥ 75 years, and LVEF <50 versus
225 $\geq 50\%$.

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

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

241 **Results**

242 One hundred and 60 patients completed randomization and received at least one dose of allocated
243 treatment, with 80 in each group (**Figure 1**). The mean age was 76 years (SD 8), 46% were women
244 and 7% self-declared non-white ethnicity. The majority of patients at baseline had either moderate
245 troubling symptoms without effect on daily activity (mEHRA class 2b; 47%), or severe symptoms
246 that did impair daily activity (mEHRA class 3; 40%). Mean NYHA class was 2.4 (SD 0.6), with
247 52% having signs of heart failure on clinical examination. Median NTpro-BNP was 1057 pg/mL
248 (IQR 744-1522) and 19% of patients had LVEF <50% on echocardiography. Groups were well
249 balanced at baseline (**Table 1**), with the exception of more signs of heart failure in those
250 randomized to digoxin. Mean heart rate on the baseline 12-lead ECG was 100 beats/min (SD 18)
251 and was not different between groups. Apart from one patient with an absolute contraindication, all
252 other patients were receiving oral anticoagulants by the end of uptitration.

253
254 At 6-months, 73 out of 76 patients (96%) randomized to digoxin were still taking the drug, with a
255 mean dose of 161 mcg (SD 55) and digoxin level of 0.78 ng/mL (SD 0.31). In the beta-blocker
256 group, 66 of 74 patients (89%) were still taking beta-blockers at six months, comprising of 59 still
257 receiving bisoprolol (80%) with a mean dose of 3.2 mg, and 7 (9%) who had switched to alternative
258 beta-blockers due to adverse events. Use of study drugs was similar at 12-months (**Supplement 3,**
259 **eTable 1**). Over the course of the trial, 5 patients (6.8%) required an additional rate control drug in
260 the digoxin group, compared to 1 patient (1.4%) randomized to beta-blockers. At 12-months, 7
261 patients (4.8%) were found to be in sinus rhythm (2 digoxin, 5 beta-blockers), 3 had withdrawn and
262 1 could not attend follow-up (**Figure 1**), with vital status known for all patients. Heart rate
263 responded similarly in both groups over time (**Supplement 3, eFigure 2**). A higher 24-hour heart
264 rate in the digoxin group was noted following uptitration at a mean of 3.1 (SD 2.0) months (AMD
265 4.3 beats/min, 95% CI 0.7-7.9; p=0.02). There was no significant difference in resting heart rate at

266 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
267 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
268 significant difference in exercise heart rate at these time points (**Supplement 3, eTable 2**).

269

270 **Primary endpoint**

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

275

276 **Secondary endpoints**

277 Quality of life: At baseline, QoL was substantially lower than the norm for the UK population in
278 SF36 domains related to physical or functional assessment (**Supplement 3, eFigure 4**). There were
279 no significant differences between digoxin and beta-blockers for SF36 domains at 6-months (**Table**
280 **3 and Supplement 3, eTable 3**). At 12-months, patients randomized to digoxin had significantly
281 better normalized SF36 scores for Vitality (AMD 3.9, 0.8-7.0; p=0.01), General Health (AMD 2.8,
282 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,
283 0.0-6.9; p=0.05) compared to beta-blockers. There was no statistically significant difference in
284 other domains or summaries, including the SF36-PCS (AMD 1.6, -1.4 to 4.7; p=0.29). The EQ-5D-
285 5L visual analogue score was also significantly better in the digoxin group by 12-months (AMD
286 5.45, 0.30 to 10.61; p=0.04). The AFEQT overall score was not different at either 6 or 12-months.

287

288 Symptoms & functional outcomes: The mEHRA functional classification score was substantially
289 better in the digoxin group at follow-up, with 53% of patients reporting a two-class improvement at
290 6-months, compared to 9% for beta-blockers (adjusted OR 10.3, 4.0 to 26.6; p<0.001). The

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

297 Cardiac function: Median NTproBNP in the digoxin group decreased from 1095 pg/mL (715-1527)
298 to 1057.5 (626-1531) in the first 6-months, then to 960 (626-1531) at 12-months. In contrast,
299 NTproBNP increased in the beta-blocker group from 1041 pg/mL (753-1480) to 1209 (837-1531) at
300 6-months, and to 1250 (847-1890) at 12-months. There was no significant difference between
301 groups at 6-months (ratio of geometric means 0.85, 0.70-1.03; $p=0.09$), but statistical significance
302 was reached by 12-months (ratio 0.77, 0.64-0.92; $p=0.005$; **Table 3**). Mean LVEF increased in
303 both groups, with no statistically significant difference between digoxin and beta-blockers for
304 systolic or diastolic function at 12-months (**Table 3**).

305

306 **Post-hoc endpoints**

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

309 Treatment with digoxin was associated with significantly lower NYHA class at both 6-months
310 (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
311 versus 2.0 ± 0.6 ; AMD -0.6, -0.8 to -0.4; $p<0.001$); **Supplement 3, eFigure 5**.

312

313 **Adverse events**

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

316 blockers (Chi-squared=24.91; $p<0.001$). The total number of treatment-related adverse events was
317 29 in the digoxin group, versus 142 with beta-blockers, with post-hoc incidence rate ratio (IRR)
318 0.30, 95% CI 0.15 to 0.59; $p<0.001$. The total number of adjudicated serious adverse events was 16
319 with digoxin therapy versus 37 with beta-blockers. Three adjudicated cardiovascular events
320 occurred in 2 patients in the digoxin group, compared to 15 events in 12 patients for beta-blockers.
321 Four patients died in those randomized to digoxin (5.0%) and 7 with beta-blockers (8.8%), with one
322 death (1.3%) and four deaths (5.0%) respectively related to cardiovascular causes. There were
323 fewer visits to primary care in the digoxin group related to either AF or another cardiovascular
324 cause. No pacing devices were required in patients randomized to digoxin (0.0%), compared to 3
325 with beta-blockers (4.2%; of which 2 [2.7%] were for bradycardia indications). Pauses on the 24-
326 hour recording occurred in 33% in those randomized to digoxin (mean duration of the longest pause
327 2.8 ± 0.4 seconds) and 39% in the beta-blocker group (3.2 ± 1.9 seconds).

328

329

330 Discussion

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

335
336 This trial was designed to address a major evidence-gap in the management of patients with AF,
337 with outcomes of concern to patients in this growing population.²¹ Heart rate control is often the
338 sole treatment for impaired QoL In in the context of permanent AF, where there has been a joint
339 decision by the patient and physician not to pursue attempts at restoring normal sinus rhythm. heart
340 rate control is often the sole treatment for impaired QoL. Without adequate RCTs, clinicians have
341 relied on anecdotal experience to guide rate control therapy, often defaulting to beta-blockers in
342 routine practice. Despite the long history of digoxin²², non-acute RCTs are only available in the
343 context of heart failure with sinus rhythm.¹² The mechanism of action of digoxin is proposed to
344 include neurohormonal components (anti-adrenergic/pro-vagal), electrophysiological (increased
345 atrioventricular node refractory period), cellular (inhibition of sodium-potassium ATPase), and
346 resultant hemodynamic changes.¹³ Beta-adrenergic blockers have been widely studied across
347 different cardiovascular indications, but again there is a lack of data specifically in those with AF.⁹
348 In an individual patient-level meta-analysis of the landmark double-blind HFrEF RCTs, beta-
349 blockers substantially reduced all-cause mortality in sinus rhythm (hazard ratio 0.73; 95% CI 0.67-
350 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;
351 p=0.73; n=3,063).⁷ The distinct relationship in AF between heart rate and prognosis may contribute
352 to this difference in efficacy.²³ In the only major RCT comparing heart rate targets in AF, strict
353 heart rate control (predominantly using beta-blockers) did not reduce a composite of clinical events
354 compared to lenient control.²⁴

355

356 This trial was designed with a two-sided hypothesis for the primary outcome to detect 0.5 SD
357 difference in SF36-PCS. This approach was chosen as 0.5 SD is consistently reflective of the
358 MCID across a range of diseases.¹⁹ MCIDs for SF36 vary according to the methodology involved
359 (criterion, anchor-based or distributional) as well as the disease; in a study of 31,325 Medicare
360 patients with heart failure published by the instrument developers, the MCID for SF36-PCS was 4.1
361 corresponding to a 20% increased mortality risk, and 9.2 for a 50% increase.¹⁷ In independent
362 studies, MCIDs of 5.5 for SF36-PCS have been suggested for cervical myelopathy²⁵, for knee
363 arthritis 10²⁶, rheumatoid arthritis 7.2²⁷, pulmonary fibrosis 5.0²⁸ and carotid artery disease 8.2.²⁹
364 Although MCID approaches have been criticized³⁰, these ranges are consistent with clinical
365 correlates seen in rhythm control trials of patients with AF (**Supplement 3, eTable 6**), including a
366 recent study where an 8.9 score difference in SF36 general health had clinical relevance.³¹ The
367 upper 95% confidence limit for the primary outcome comparing digoxin with beta-blockers in this
368 trial was 3.9, suggesting that the difference in effect of these drugs on SF36-PCS at 6-months
369 (adjusted for baseline score) is not a clinically-important difference.

370

371 Secondary endpoints should be considered as exploratory and hypothesis generating; by 12-months,
372 8/20 outcomes were significantly different (all favoring digoxin) and 12 null, with better symptom
373 control with digoxin for both AF and heart failure-related symptoms consistent with a significantly
374 lower NTproBNP and adverse events compared to the beta-blocker group. There was no
375 requirement for pacemakers, no increase in pauses and no deterioration in LVEF with digoxin
376 therapy, and in contrast to short-term RCTs, there was no statistically significant difference
377 compared to beta-blockers in longer-term heart rate. Concerns in the use of digoxin, such as the
378 narrow therapeutic window and drug interactions were not an issue in this low-dose approach.

379

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

381 diagnosis in AF, both for HF_rEF (where there is no data on the validity of measuring systolic
382 function in AF³²) and also heart failure with preserved LVEF (where symptomatic improvement
383 using diuretics may be required to separate overlapping diagnostic features⁵). The majority of
384 patients in the trial also had other comorbidities, with patient focus groups suggesting that benefit to
385 AF-related symptoms was often offset by enhanced appreciation of these comorbidities (particularly
386 large-joint arthritis) leading to a neutral effect on overall QoL.²¹ This may explain why no
387 significant difference between groups was identified for summary QoL domains and 6MWD, which
388 highlights the importance of broad and inclusive management of patients with AF⁸ and an
389 integrated management approach.³³

390

391 **Limitations**

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

406

407

408 **Conclusions**

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

413

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425 www.birmingham.ac.uk/rate-af.

426

427 **Data Sharing Statement**

428 See Supplement 4.

429

430 **Access to Data**

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

434

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436 Neither the Sponsor (University of Birmingham) nor the Funder (UK National Institute for Health
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441

442 **Competing interests**

443 All authors have completed the ICMJE uniform disclosure form

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474

475 **Authors' contributions**

476 The manuscript was drafted by DK who is the Chief Investigator for the RATE-AF trial, with the
477 assistance of the Patient and Public Involvement Team (MS, JJ and SH). KVB and SKG were the
478 research assistants, SM the trial statistician, and MG, JNT and GYHL the Principal Investigators.
479 AJC was the independent chair of the Trial Steering Committee; KR the independent chair of the
480 Data Monitoring Committee, and VYS the independent statistician. All other authors listed were
481 ~~either~~ members of the Trial Management Group ~~or the Oversight Committees~~. All authors
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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 Heart 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 Heart 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) ^c	<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.