Clinical trial results:
Evaluating different rate control therapies in permanent atrial fibrillation: A prospective, randomised, open-label, blinded endpoint study comparing digoxin and beta-blockers as initial rate control therapy. RAte control Therapy Evaluation in permanent Atrial Fibrillation: RATE-AF

Summary

EudraCT number	2015-005043-13
Trial protocol	GB
Global end of trial date	26 February 2020
Results information	
Result version number	v1 (current)
This version publication date	14 April 2021
First version publication date	14 April 2021

Trial information

Trial identification	
Sponsor protocol code	RG_14-187
Additional study identifiers	
ISRCTN number	ISRCTN95259705
ClinicalTrials.gov id (NCT number)	NCT02391337
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	University of Birmingham
Sponsor organisation address	Aston Webb Building , Birmingham, United Kingdom, B15 2TT
Public contact	Dipak Kotecha, University of Birmingham, +44 (0) 7974 115676, d.kotecha@bham.ac.uk
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Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2019
Global end of trial reached?	Yes
Global end of trial date	26 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Patient-reported quality of life (QoL), with a predefined focus on physical well-being using the SF-36 (a QoL tool) physical component summary at six months.

Protection of trial subjects:

All sites were provided with the Rate-AF protocol that provided specific instruction relating to inclusion/exclusion criteria and trial patient safety. There was clear instruction relating to trial intervention safety and considerations detailed within the protocol. Rate-AF had a Data Monitoring Committee to monitor patient safety throughout the trial.

Background therapy:

Atrial fibrillation is a common heart rhythm disturbance, causing discomfort for patients, a high risk of stroke, frequent hospital admissions and a two-fold increase in death. The number of patients with this condition are expected to double in the next 20 years. Medications to control heart-rate are used in the majority of patients, although the choice of agent is often guided by local preference rather than evidence from controlled trials. Despite the fact that patients with atrial fibrillation have high rates of other cardiac conditions such as heart failure, clinicians have insufficient evidence to personalise the use of different therapies. This feasibility study allowed us to develop a range of methods that could characterise patients according to the pumping and relaxing function of the heart, the burden of symptoms and to identify new blood markers. In this way, the investigators hoped to improve clinical practice guidelines, allowing doctors to prescribe appropriate treatments for the right patients.
The research focused around a randomised trial of two medication strategies, providing much-needed data on the comparison of digoxin and beta-blockers (two commonly-used drugs in patients with atrial fibrillation). It also allowed us to identify the best way to record patient-reported quality of life and develop robust techniques to determine heart function using non-invasive imaging, facilitating the conduct of a large-scale clinical trial. The key objectives of the research programme were to define the optimal medications for patients with atrial fibrillation and identify the most valid, reproducible and cost-effective methods to examine patients. The ultimate aim of the project was to improve clinical outcomes in atrial fibrillation, benefiting patients, the National Health Service and the global community.

Evidence for comparator:

A prospective, randomised, open-label, blinded-endpoint (PROBE) study design. Recruited patients will receive either:
Digoxin- The maintenance dose of oral digoxin will be either 62.5µg or 125µg according to the pre-defined treatment schedule and up titrated, as required, to 250µg daily. A single loading dose of four tablets (250 or 500µg according to target maintenance dose) will be prescribed in digoxin-naïve participants, where necessary OR
Beta-blocker- Oral bisoprolol will be commenced at either 1.25mg, 2.5mg or 5mg according to the treatment schedule and uptitrated, as required, to 15mg daily.
Patients will be followed-up for the duration of treatment.

Actual start date of recruitment	20 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 161
Worldwide total number of subjects	161
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	117
85 years and over	29

Subject disposition

Recruitment

Recruitment details:

First patient was randomised on the 20th December 2016 and the last patient was randomised on the 01st October 2018. A total of 161 patients were randomised into the Rate-AF Trial across one centre. Patients were equally recruited with 80 patients in the Bisoprolol arm and 81 in the Digoxin arm.

Pre-assignment

Screening details:

A total of 390 were screened for the trial, of these screened 161 were randomised.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

Arms

Are arms mutually exclusive?	Yes
Arm title	Digoxin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Digoxin Tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Trial maintenance doses will initially be 62.5 or 125 µg orally (at the clinician's discretion, taking into account age and renal function), with planned up-titration to 125/250 µg. The maximum trial dose will be 250 µg daily.

A single loading dose of four tablets (250 or 500 µg according to target maintenance dose) will be prescribed in digoxin-naïve participants. The clinician is permitted to omit the loading dose or prescribe a second, where necessary.

Unblinded serum digoxin concentrations will be assessed at visits 2 and 3, with results reported back to the relevant clinician(s). This process will assist in monitoring compliance, adjusting dosage in cases of low serum levels and avoiding toxicity.

Arm title	Bisoprolol

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Bisoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Trial starting doses will be 1.25 or 2.5 or 5 mg (at the clinician's discretion), with planned up-titration to 10 mg in increments of 1.25 or 2.5 mg. The maximum trial dose will be 15 mg daily. No loading dose is required.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Blinding implementation details: A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

Number of subjects in period 1	Digoxin	Bisoprolol
Started	81	80
Completed	81	80

Period 2

Period 2 title	6 months follw-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[2]

Blinding implementation details:

A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

Arms

Are arms mutually exclusive?	Yes
Arm title	Digoxin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Digoxin Tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Trial maintenance doses will initially be 62.5 or 125 µg orally (at the clinician's discretion, taking into account age and renal function), with planned up-titration to 125/250 µg. The maximum trial dose will be 250 µg daily.

A single loading dose of four tablets (250 or 500 µg according to target maintenance dose) will be prescribed in digoxin-naïve participants. The clinician is permitted to omit the loading dose or prescribe a second, where necessary.

Unblinded serum digoxin concentrations will be assessed at visits 2 and 3, with results reported back to the relevant clinician(s). This process will assist in monitoring compliance, adjusting dosage in cases of

low serum levels and avoiding toxicity.

Arm title	Bisoprolol
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Bisoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Trial starting doses will be 1.25 or 2.5 or 5 mg (at the clinician's discretion), with planned up-titration to 10 mg in increments of 1.25 or 2.5 mg. The maximum trial dose will be 15 mg daily. No loading dose is required.

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Blinding implementation details: A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

Number of subjects in period 2	Digoxin	Bisoprolol
Started	81	80
Completed	76	74
Not completed	5	6
Adverse event, serious fatal	4	5
Consent withdrawn by subject	1	1

Period 3

Period 3 title	12 month follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[3]

Blinding implementation details:

A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

Arms

Are arms mutually exclusive?	Yes

Arm title	Digoxin
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Digoxin Tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Trial maintenance doses will initially be 62.5 or 125 µg orally (at the clinician's discretion, taking into account age and renal function), with planned up-titration to 125/250 µg. The maximum trial dose will be 250 µg daily.

A single loading dose of four tablets (250 or 500 µg according to target maintenance dose) will be prescribed in digoxin-naïve participants. The clinician is permitted to omit the loading dose or prescribe a second, where necessary.

Unblinded serum digoxin concentrations will be assessed at visits 2 and 3, with results reported back to the relevant clinician(s). This process will assist in monitoring compliance, adjusting dosage in cases of low serum levels and avoiding toxicity.

Arm title	Bisoprolol
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Bisoprolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Trial starting doses will be 1.25 or 2.5 or 5 mg (at the clinician's discretion), with planned up-titration to 10 mg in increments of 1.25 or 2.5 mg. The maximum trial dose will be 15 mg daily. No loading dose is required.

Notes:

[3] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Blinding implementation details:
A prospective, randomised, open-label, blinded endpoint trial comparing digoxin and beta-blockers as initial rate control therapy with investigator blinded endpoint. A prospective, randomised, open-label, blinded-endpoint (PROBE) study design.

Number of subjects in period 3	Digoxin	Bisoprolol
Started	76	74
Completed	73	72
Not completed	3	2
Adverse event, serious fatal	-	2
Consent withdrawn by subject	1	-
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Digoxin
Reporting group description: -	
Reporting group title	Bisoprolol
Reporting group description: -	

Reporting group values	Digoxin	Bisoprolol	Total
Number of subjects	81	80	161
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	4	15
From 65-84 years	59	58	117
85 years and over	11	18	29
Age continuous Units: years			
arithmetic mean	74.4	76.8	
standard deviation	± 8.4	± 8.1	-
Gender categorical Units: Subjects			
Female	36	38	74
Male	45	42	87
On anticoagulant before randomisation Units: Subjects			
No	9	17	26
Yes	72	63	135
EHRA class			
*Minimisation variables Note: EHRA Class was categorised into (Class 1, 2a) and (Class 2b, 3, 4) for the minimisation algorithm			
Units: Subjects			
Cat 1	0	0	0
Cat 2a	3	3	6
Cat 2b	35	40	75
Cat 3	38	27	65
Cat 4	5	10	15
NYHA class Units: Subjects			
Class I	0	0	0
Class II	47	53	100
Class III	32	24	56

Class IV	2	3	5
Previous diagnosis of heart failure? Units: Subjects			
No	46	56	102
Yes	35	24	59
Any signs of heart failure at baseline Units: Subjects			
No	32	45	77
Yes	49	35	84
Type I diabetes Units: Subjects			
No	81	80	161
Yes	0	0	0
Type II diabetes Units: Subjects			
No	65	58	123
Yes	16	22	38
Unplanned admission for AF or HF in last 12 months Units: Subjects			
No	65	65	130
Yes	16	15	31
Any previous cardioversions Units: Subjects			
No	74	71	145
Yes	7	9	16
Previously undergone AF ablation Units: Subjects			
No	79	79	158
Yes	2	1	3
Previous history of anti-arrhythmic drugs Units: Subjects			
No	75	72	147
Yes	6	8	14
Self-declared ethnicity Units: Subjects			
White - English / Welsh / Scottish / Northern Iris	72	66	138
White - Irish	4	8	12
Asian / Asian British – Indian	3	2	5
Asian / Asian British – Pakistani	0	3	3
Black / African / Caribbean / Black British – Afri	0	1	1
Black / African / Caribbean / Black British – Cari	2	0	2
Creatinine Units: (micromol/L)			
arithmetic mean	87.9	91.4	
standard deviation	± 25.1	± 23.1	-
Baseline NTproBNP Units: (pg/mL)			
arithmetic mean	1473.3	1339.2	

standard deviation	± 2134	± 1107.5	-
Radial artery heart rate Units: bpm			
arithmetic mean	87.8	86.9	
standard deviation	± 12	± 10.3	-
Apex beat heart rate Units: bpm			
arithmetic mean	98.3	99	
standard deviation	± 15.1	± 16.8	-
12-Lead ECG Heart Rate Units: bpm			
arithmetic mean	100.3	99.2	
standard deviation	± 16.8	± 19.2	-
Systolic BP Units: mmHg			
arithmetic mean	134.5	137.1	
standard deviation	± 14.9	± 17.5	-
Estimated ejection fraction Units: Percentage			
arithmetic mean	56.2	57.6	
standard deviation	± 8.8	± 10.5	-

End points

End points reporting groups

Reporting group title	Digoxin
Reporting group description: -	
Reporting group title	Bisoprolol
Reporting group description: -	
Reporting group title	Digoxin
Reporting group description: -	
Reporting group title	Bisoprolol
Reporting group description: -	
Reporting group title	Digoxin
Reporting group description: -	
Reporting group title	Bisoprolol
Reporting group description: -	

Primary: Primary outcome- SF36v2 PCS

End point title	Primary outcome- SF36v2 PCS[1]
End point description:	
The primary outcome is the SF-36v2 physical component summary (PCS) score at 6 months.	
End point type	Primary
End point timeframe:	
6 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The CI instructed that we do not provide the analyses and just to enter the minimum fields only. Full analysis result has already been published in the paper, Jama.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	76	74
Units: Score				
arithmetic mean (standard deviation)	28.9 (± 11.6)	27.2 (± 10.2)	31.9 (± 11.7)	29.7 (± 11.4)

Statistical analyses

No statistical analyses for this end point

Secondary: SF36v2 Physical Component Summary (PCS)

End point title	SF36v2 Physical Component Summary (PCS)
End point description:	
End point type	Secondary
End point timeframe:	
6 and 12 months	

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	72	72
Units: score				
arithmetic mean (standard deviation)	28.9 (± 11.6)	27.2 (± 10.2)	32.5 (± 13)	29.4 (± 12.4)

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2 Mental Component Summary (MCS)

End point title	SF-36v2 Mental Component Summary (MCS)

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	76	74
Units: Score				
arithmetic mean (standard deviation)	50.4 (± 10.2)	49.5 (± 10)	51.1 (± 10.6)	50 (± 10.4)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	72		
Units: Score				
arithmetic mean (standard deviation)	53.6 (± 8.9)	51.3 (± 10.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2 Physical Function Domain Score (PF)

End point title	SF-36v2 Physical Function Domain Score (PF)

End point description:

End point type	Secondary

End point timeframe:
Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: Score				
arithmetic mean (standard deviation)	26.8 (± 12.6)	25.9 (± 12.2)	29.2 (± 13.7)	27.7 (± 13.6)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: Score				
arithmetic mean (standard deviation)	31.5 (± 14.1)	27.5 (± 13)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36 Role Limitation Due to Physical Domain score (RP)

End point title	SF-36 Role Limitation Due to Physical Domain score (RP)

End point description:

End point type	Secondary

End point timeframe:
Baseline, 6 and 12 months

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	76	74
Units: Score				
arithmetic mean (standard deviation)	31.8 (± 12.6)	29.6 (± 12.1)	34.2 (± 12)	31.3 (± 12.8)

End point values	Digoxin	Bisoprolol		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: Score				
arithmetic mean (standard deviation)	37 (± 12.6)	32 (± 12.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36 Role Limitation Due to Emotional Problems Domain score (RE)

End point title	SF-36 Role Limitation Due to Emotional Problems Domain score (RE)

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 .

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: Score				
arithmetic mean (standard deviation)	40.2 (± 14.3)	39.8 (± 15)	42 (± 13.3)	38.7 (± 14.9)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: Score				
arithmetic mean (standard deviation)	45.2 (± 12.9)	40.7 (± 15.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2 Social Functioning Domain Score (SF)

End point title	SF-36v2 Social Functioning Domain Score (SF)

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	76	74
Units: Score				
arithmetic mean (standard deviation)	42.8 (± 12.3)	41.3 (± 12)	46.1 (± 11.5)	43.5 (± 12.5)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: Score				
arithmetic mean (standard deviation)	45.6 (± 12.3)	43.3 (± 11.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2 Mental Health Domain (MH)

End point title	SF-36v2 Mental Health Domain (MH)

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: Score				
arithmetic mean (standard deviation)	48 (± 11.6)	48.2 (± 9.5)	48.2 (± 10.7)	49.4 (± 11.2)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: Score				
arithmetic mean (standard deviation)	51.3 (± 9.3)	51.8 (± 9.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2 Energy/Vitality Domain Score (EV)

End point title	SF-36v2 Energy/Vitality Domain Score (EV)

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: Score				
arithmetic mean (standard deviation)	43.4 (± 9.6)	40.3 (± 10)	44.9 (± 10.4)	43 (± 10)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: Score				
arithmetic mean (standard deviation)	47.1 (± 9.9)	42 (± 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2- Pain Score (Pain)

End point title	SF-36v2- Pain Score (Pain)

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	76	74
Units: Score				
arithmetic mean (standard deviation)	39.1 (± 12.2)	37.5 (± 10.9)	42 (± 12.1)	41 (± 11.6)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: Score				
arithmetic mean (standard deviation)	40.5 (± 12.7)	41.9 (± 12.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36v2- General Health Perception Domain Score (GHP)

End point title	SF-36v2- General Health Perception Domain Score (GHP)

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: Score				
arithmetic mean (standard deviation)	40.5 (± 9.4)	39 (± 9.4)	41.6 (± 9.6)	40 (± 9.8)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	72		
Units: Score				
arithmetic mean (standard deviation)	42.8 (± 9.9)	39.6 (± 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L summary index score

End point title	EQ-5D-5L summary index score

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: Score				
arithmetic mean (standard deviation)	0.67 (± 0.19)	0.63 (± 0.22)	0.66 (± 0.27)	0.65 (± 0.23)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: Score				
arithmetic mean (standard deviation)	0.66 (± 0.27)	0.62 (± 0.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L visual analogue scale (VAS) score

End point title	EQ-5D-5L visual analogue scale (VAS) score

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: Score				
arithmetic mean (standard deviation)	64 (± 16.6)	61.6 (± 20.3)	71.8 (± 16.3)	68.5 (± 17.1)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: Score				
arithmetic mean (standard deviation)	72.2 (± 17)	66.2 (± 17.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: AFEQT overall score

End point title	AFEQT overall score

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: Score				
arithmetic mean (standard deviation)	62.2 (± 16.7)	57.2 (± 17.6)	72.1 (± 17.9)	65.6 (± 16.8)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: Score				
arithmetic mean (standard deviation)	75.6 (± 17.1)	68.1 (± 16.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Echocardiographic LVEF

End point title	Echocardiographic LVEF

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	73	72
Units: Score				
arithmetic mean (standard deviation)	56.2 (± 8.8)	57.6 (± 10.5)	59.7 (± 8.7)	59.8 (± 7.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Diastolic Function E/e

End point title	Diastolic Function E/e

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	73	72
Units: Score				
arithmetic mean (standard deviation)	10.7 (± 4.5)	10.2 (± 4.7)	10.8 (± 5.1)	10.8 (± 5.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Composite of diastolic indices

End point title	Composite of diastolic indices

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	73	72
Units: Percentages				
No	68	72	65	65
Yes	13	8	8	7

Statistical analyses

No statistical analyses for this end point

Secondary: Radial Heart Rate (bpm)

End point title	Radial Heart Rate (bpm)

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: bpm				
arithmetic mean (standard deviation)	87.8 (± 12)	86.9 (± 10.3)	76.2 (± 9.7)	73.9 (± 10.8)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: bpm				
arithmetic mean (standard deviation)	76 (± 9)	73.8 (± 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apical Heart rate

End point title	Apical Heart rate

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: bpm				
arithmetic mean (standard deviation)	98.3 (± 15.1)	99 (± 16.8)	78.4 (± 10.5)	76.2 (± 11.1)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: bpm				
arithmetic mean (standard deviation)	78.3 (± 9.2)	76.2 (± 10.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: 12-lead ECG Heart rate (bpm)

End point title	12-lead ECG Heart rate (bpm)

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: bpm				
arithmetic mean (standard deviation)	100.3 (± 16.8)	99.2 (± 19.2)	76.9 (± 12.1)	74.8 (± 11.6)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: bpm				
arithmetic mean (standard deviation)	75.4 (± 9.9)	74.3 (± 11.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: 24-hour ambulatory average Heart rate (bpm)

End point title	24-hour ambulatory average Heart rate (bpm)

End point description:

This measurement was just done once. Change in heart rate using 24-hour ambulatory ECG.

End point type	Secondary

End point timeframe:

24-hour time period

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	78		
Units: bpm				
arithmetic mean (standard deviation)	78.9 (± 11.3)	73.7 (± 10.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Distance covered (in metres) from the six-minute walk test

End point title	Distance covered (in metres) from the six-minute walk test

End point description:

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	79	74	73
Units: Metres				
median (inter-quartile range (Q1-Q3))	321 (120 to 419)	330 (90 to 450)	335.5 (180 to 422)	348 (180 to 431)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	69		
Units: Metres				
median (inter-quartile range (Q1-Q3))	366 (233 to 435)	329 (120 to 429)		

Statistical analyses

No statistical analyses for this end point

Secondary: NTproBNP

End point title	NTproBNP

End point description:

End point type	Secondary

End point timeframe:
Baseline, 6 and 12 months.

End point values	Digoxin	Bisoprolol	Digoxin	Bisoprolol
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	80	76	74
Units: ng/L				
median (inter-quartile range (Q1-Q3))	1091 (710 to 1522)	1040.5 (752.5 to 1480)	1057.5 (625.5 to 1531)	1209 (837 to 1531)

End point values	Digoxin	Bisoprolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: ng/L				
median (inter-quartile range (Q1-Q3))	960 (626 to 1531)	1249.5 (847 to 1890)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Targeted AEs reported on the CRF were reportable to the RATE-AF Trial Office up to 30 days post last IMP administration. Any SUSAR related to the IMP was expected to be reported irrespective of how long after IMP administration the reaction has occurred.

Adverse event reporting additional description:

Adverse events (AEs) were recorded in the medical records and CRFs. Most AE/ARs that occurred in the trial, whether they are serious or not, were 'expected' treatment-related toxicities due to the drugs used in this trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Digoxin
Reporting group description: -	
Reporting group title	Bisoprolol

Reporting group description: -

Serious adverse events	Digoxin	Bisoprolol	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 81 (16.05%)	21 / 80 (26.25%)	
number of deaths (all causes)	4	7	
number of deaths resulting from adverse events	4	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary Malignancy			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 81 (2.47%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Vascular disorders			
Haemorrhage/Bleeding			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular			
subjects affected / exposed	0 / 81 (0.00%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Constitutional Symptoms			
subjects affected / exposed	1 / 81 (1.23%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Pulmonary/Upper Respiratory			
subjects affected / exposed	1 / 81 (1.23%)	4 / 80 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac Arrhythmia			
subjects affected / exposed	1 / 81 (1.23%)	3 / 80 (3.75%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac general			
subjects affected / exposed	1 / 81 (1.23%)	4 / 80 (5.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 81 (1.23%)	2 / 80 (2.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 2	
Nervous system disorders			
Pain			

subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurology			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphatics			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	1 / 81 (1.23%)	3 / 80 (3.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Hepatobiliary/Pancreas			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatology/Skin			

subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal/Genitourinary			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 81 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal/Soft Tissue			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	0 / 81 (0.00%)	4 / 80 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Digoxin	Bisoprolol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 81 (24.69%)	51 / 80 (63.75%)	
Cardiac disorders			
Symptomatic bradycardia			
subjects affected / exposed	0 / 81 (0.00%)	5 / 80 (6.25%)	
occurrences (all)	0	5	
Symptomatic hypotension			
subjects affected / exposed	0 / 81 (0.00%)	6 / 80 (7.50%)	
occurrences (all)	0	7	

General disorders and administration site conditions			
Peripheral oedema			
subjects affected / exposed	1 / 81 (1.23%)	11 / 80 (13.75%)	
occurrences (all)	1	12	
Dizziness			
subjects affected / exposed	4 / 81 (4.94%)	24 / 80 (30.00%)	
occurrences (all)	4	28	
Headache			
subjects affected / exposed	5 / 81 (6.17%)	9 / 80 (11.25%)	
occurrences (all)	5	11	
Lethargy			
subjects affected / exposed	7 / 81 (8.64%)	30 / 80 (37.50%)	
occurrences (all)	7	37	
Eye disorders			
Blurred Vision			
subjects affected / exposed	2 / 81 (2.47%)	1 / 80 (1.25%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Gastrointestinal upset			
subjects affected / exposed	5 / 81 (6.17%)	8 / 80 (10.00%)	
occurrences (all)	5	8	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract symptoms			
subjects affected / exposed	1 / 81 (1.23%)	13 / 80 (16.25%)	
occurrences (all)	1	15	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 81 (1.23%)	0 / 80 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2017	Addition of new site.
29 May 2018	* Changes made to protocol. * Changes made to Participant Optional Consent Form. New documents submitted: - Optional Sub Study 'Nerve Activity and Heart Rate' Patient information leaflet. - Optional Sub Study 'Physical Activity and Heart Rate Monitoring' Patient information leaflet.
21 November 2019	Change of Principle Investigator.
13 December 2019	Changes made to protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported.

Notes: