Clinical trial results:
A trial to compare the effects of nebivolol versus atenolol on various cardiovascular measurements including insulin sensitivity

Summary

EudraCT number	2005-001214-40
Trial protocol	GB
Global end of trial date	21 January 2009

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	cro085

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00125853
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	Professor Neil Poulter, Imperial College London, +44 (0)20 7594 3446, n.poulter@imperial.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	05 July 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 January 2009
Global end of trial reached?	Yes
Global end of trial date	21 January 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of nebivolol and atenolol on insulin sensitivity

Protection of trial subjects:

Bendroflumethiazide 2.5mg daily throughout the whole study period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	27
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The participants were recruited from the Peart-Rose Hypertension clinic at St Mary's Hospital in West London and from local general practices between 2006 and 2009.

Pre-assignment

Screening details:

55 patients with mild-to-moderate essential hypertension were recruited, 54 participants were randomized.

Period 1

Period 1 title	Wash out
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nebivolol_before treatment

Arm description:

Participants randomized to Nebivolol as a first treatment. Wash-out period participants received Bendroflumethiazide for 4 weeks.

Arm type	wash-out
Investigational medicinal product name	Bendroflumethiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg daily for 4 weeks

Arm title	Atenolol_before treatment

Arm description:

Participants randomized to Atenolol as a first treatment. Wash-out period participants received Bendroflumethiazide for 4 weeks.

Arm type	wash-out
Investigational medicinal product name	Bendroflumethiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg daily for 4 weeks

Number of subjects in period 1	Nebivolol_before treatment	Atenolol_before treatment
Started	27	27
Completed	27	27

Period 2	
Period 2 title	First treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms	
Are arms mutually exclusive?	Yes
Arm title	Atenolol

Arm description:
Participants received Atenolol and Bendroflumethiazide for 8 weeks

Arm type	Experimental
Investigational medicinal product name	Bendroflumethiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
2.5mg daily for 8 weeks

Investigational medicinal product name	Atenolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
25mg daily for 8 weeks

Arm title	Nebivolol

Arm description:
participants received Nebivolol and Bendroflumethiazide for 8 weeks

Arm type	Experimental
Investigational medicinal product name	Bendroflumethiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
2.5mg daily for 8 weeks

Investigational medicinal product name	Nebivolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg daily for 8 weeks

Number of subjects in period 2	Atenolol	Nebivolol
Started	27	27
Completed	27	27

Period 3

Period 3 title	Wash out
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All participants

Arm description:

All participants received Bendroflumethiazide for 4 weeks.

Arm type	wash-out
Investigational medicinal product name	Bendroflumethiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg daily for 4 weeks

Number of subjects in period 3	All participants
Started	54
Completed	44
Not completed	10
Lost to follow-up	10

Period 4

Period 4 title	Second intervention
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Nebivolol

Arm description:

Participants received Nebivolol and Bendroflumethiazide for 8 weeks

Arm type	Experimental
Investigational medicinal product name	Nebivolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg daily for 8 weeks

Investigational medicinal product name	Bendroflumethiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg daily for 8 weeks

Arm title	Atenolol

Arm description:

Participants received Atenolol and Bendroflumethiazide for 8 weeks

Arm type	Experimental
Investigational medicinal product name	Bendroflumethiazide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5mg daily for 8 weeks

Investigational medicinal product name	Atenolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25mg daily for 8 weeks

Number of subjects in period 4	Nebivolol	Atenolol
Started	20	24
Completed	20	24

Baseline characteristics

Reporting groups	
Reporting group title	Wash out

Reporting group description: -

Reporting group values	Wash out	Total	
Number of subjects	54	54	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
geometric mean	61.1		
standard deviation	± 11	-	
Gender categorical Units: Subjects			
Female	29	29	
Male	25	25	
BMI Units: kg/m^2			
geometric mean	27.2		
standard deviation	± 6.7	-	
Systolic Blood Pressure (SBP) Units: mmHg			
geometric mean	129.4		
standard deviation	± 13.2	-	
Diastolic Blood Pressure (DBP) Units: mmHg			
geometric mean	81.3		
standard deviation	± 9	-	
HBa1c Units: percentage of glycosylated hemoglobin			
geometric mean	5.7		
standard deviation	± 0.7	-	
Total Cholesterol Units: mmol/L			
geometric mean	5.1		
standard deviation	± 1	-	

End points

End points reporting groups

Reporting group title	Nebivolol_before treatment
Reporting group description:	
Participants randomized to Nebivolol as a first treatment. Wash-out period participants received Bendroflumethiazide for 4 weeks.	
Reporting group title	Atenolol_before treatment
Reporting group description:	
Participants randomized to Atenolol as a first treatment. Wash-out period participants received Bendroflumethiazide for 4 weeks.	
Reporting group title	Atenolol
Reporting group description:	
Participants received Atenolol and Bendroflumethiazide for 8 weeks	
Reporting group title	Nebivolol
Reporting group description:	
participants received Nebivolol and Bendroflumethiazide for 8 weeks	
Reporting group title	All participants
Reporting group description:	
All participants received Bendroflumethiazide for 4 weeks.	
Reporting group title	Nebivolol
Reporting group description:	
Participants received Nebivolol and Bendroflumethiazide for 8 weeks	
Reporting group title	Atenolol
Reporting group description:	
Participants received Atenolol and Bendroflumethiazide for 8 weeks	
Subject analysis set title	Atenolol
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who received Atenolol treatments	
Subject analysis set title	Nebivolol
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who received Nebivolol treatments	

Primary: Insulin Sensitivity Index (ISI)

End point title	Insulin Sensitivity Index (ISI)
End point description:	
Patients were asked to fast for a minimum of 12 hours prior to each oral glucose tolerance test (OGTT). Venous blood was withdrawn for insulin and glucose analysis, 15 minutes and immediately prior to, and 30, 60, 90 and 120 minutes following an oral glucose load. For each OGTT, the Insulin Sensitivity Index (ISI) was calculated using the standard method for oral glucose tolerance testing. For each OGTT, the Insulin Sensitivity Index (ISI) was calculated using the standard method for oral glucose tolerance testing.	
End point type	Primary
End point timeframe:	
Baseline, 15, 30, 60, 90, 120 m following oral glucose load after 8 weeks treatment	

End point values	Atenolol	Nebivolol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: factor				
geometric mean (inter-quartile range (Q1-Q3))	75.47 (50.6 to 144.9)	81.54 (50.9 to 114.9)		

Statistical analyses

Statistical analysis title	Insulin Sensitivity Index (ISI)
Comparison groups	Atenolol v Nebivolol
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.6
Method	Linear Mixed effect Modelling, adjusted

Notes:

[1] - Linear Mixed effect Modelling, adjusted for baseline values and period effect

Secondary: 24 Hour Systolic Blood Pressure

End point title	24 Hour Systolic Blood Pressure

End point description:

The 24-h Ambulatory Blood Pressure Monitoring (ABPM) was recorded at the beginning and end of each beta-blocker treatment period. BP was automatically recorded for 24 h at 30 min intervals. The time periods from 0700h to 2200h and from 2200h to 0700h were defined as daytime and night-time, respectively.

End point type	Secondary

End point timeframe:

After 8 weeks of treatment

End point values	Atenolol	Nebivolol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: mmHg				
geometric mean (standard deviation)	117.2 (± 9.2)	121.2 (± 8.2)		

Statistical analyses

Statistical analysis title	24 Hour Systolic Blood Pressure
Comparison groups	Atenolol v Nebivolol

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.06
Method	Linear Mixed effect Modelling, adjusted

Notes:

[2] - Linear Mixed effect Model, adjusted for baseline values and period effect

Secondary: Total Cholesterol

End point title	Total Cholesterol

End point description:

Fasting blood samples were taken at the beginning and end of each treatment period.

End point type	Secondary

End point timeframe:

After 8 weeks of treatment

End point values	Atenolol	Nebivolol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: mmol/L				
geometric mean (standard deviation)	4.9 (± 1.0)	5.1 (± 0.9)		

Statistical analyses

Statistical analysis title	Total Cholesterol
Comparison groups	Atenolol v Nebivolol
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.51
Method	Linear Mixed effect Modelling, adjusted

Notes:

[3] - Linear Mixed effect Model, adjusted for baseline values and period effect

Secondary: HbA1c

End point title	HbA1c

End point description:

End point type	Secondary

End point timeframe:

After 8 weeks of treatment

End point values	Atenolol	Nebivolol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: percentage of glycosylated hemoglobin				
geometric mean (standard deviation)	5.7 (± 0.4)	5.7 (± 0.3)		

Statistical analyses

Statistical analysis title	HbA1c
Comparison groups	Atenolol v Nebivolol
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.48
Method	Linear Mixed effect Model, adjusted for

Notes:

[4] - Linear Mixed effect Model, adjusted for baseline values and period effect

Secondary: BMI

End point title	BMI

End point description:

End point type	Secondary

End point timeframe:

After 8 weeks of treatment

End point values	Atenolol	Nebivolol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: kg/m^2				
geometric mean (standard deviation)	28.0 (± 4.4)	28.3 (± 4.4)		

Statistical analyses

Statistical analysis title	BMI
Comparison groups	Atenolol v Nebivolol

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.09
Method	Linear Mixed effect Model, adjusted for

Notes:

[5] - Linear Mixed effect Model, adjusted for baseline values and period effect

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 32 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	Atenolol 25mg Daily
Reporting group description: -	
Reporting group title	Nebivolol 2.5mg daily
Reporting group description: -	

Serious adverse events	Atenolol 25mg Daily	Nebivolol 2.5mg daily	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	0 / 54 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Atenolol 25mg Daily	Nebivolol 2.5mg daily	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	0 / 54 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No adverse event reported

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported