Clinical trial results:
Influence of iodinated contrast agents on heart rate variation and diagnostic image quality during CT angiography of the coronary arteries

Summary

EudraCT number	2011-001419-29
Trial protocol	AT
Global end of trial date	31 December 2013

Results information

Result version number	v1 (current)
This version publication date	10 June 2021
First version publication date	10 June 2021
Summary attachment (see zip file)	manuscript entire study (report.pdf)

Trial information

Trial identification

Sponsor protocol code	HRVCTA1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Division for Cardiovascular and Interventional Radiology, Department of Bioimaging and Image Guided Therapy, +43 14040058020, christian.loewe@meduniwien.ac.at
Scientific contact	Division for Cardiovascular and Interventional Radiology, Department of Bioimaging and Image Guided Therapy, +43 14040058020, christian.loewe@meduniwien.ac.at

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	31 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2013
Global end of trial reached?	Yes
Global end of trial date	31 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To demonstrate the possibility of reducing the heart rate changes during CT angiography of the coronary arteries by selecting an iso-osmolar contrast agent

Protection of trial subjects:

the entire study was approved by the institutional review board.
patient insureance: Zürich Versicherungs AG, Schwarzenbergplatz 15, A-1010 Vienna /Austria Nr. 07229622-2
patient related date pseudonymized

Background therapy:

patients referred to Cardiac CT for the suspicion for coronary artery disease have been randomized to undergo the CT examination using one out of two iodinated contrast agents. Both agents are well established and clinically approved, but have a different molecule structure. The influence on the heart rate change and variability during the CT examination and the possible difference between the two agents should be evaluated y careful assessment of the heart rate before, during and after the CT examination. Furthermore, a possible relation to the diagnostic image quality will be evaluated by blinded reading.

Evidence for comparator:

Based on previously published data as well as based on unpublished data obtained at our own department there was some evidence of differences in the heart rate raise between the two contrast agents and a possible impact on diagnostic image quality. This was the motivation to perform this prospectively randomized trial.

1. Schroeder S, Kopp AF, Kuettner A, Burgstahler C, Herdeg C, Heuschmid M, Baumbach A, Claussen CD, Karsch KR, Seipel L. Influence of heart rate on vessel visibility in noninvasive coronary angiography using new multislice computed tomography: experience in 94 patients. Clin Imaging 2002;26(2):106-11
2. Svensson A, Ripsweden J, Ruck A, Aspelin P, Cederlund K, Brismar BT. Heart rate variability and heat sensation during CT coronary angiography: Low-osmolar versus iso-osmolar contrast media. Acta Radiol 2010;51(7):722-6.

Actual start date of recruitment	02 May 2011
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	Austria: 299
Worldwide total number of subjects	299
EEA total number of subjects	299

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)	220
From 65 to 84 years	77
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients referred for CCTA to rule out coronary artery disease (CAD) were invited to participate in this study. After an oral explanation of the content of the present study, written, informed consent was obtained from all patients. After obtaining consent, patients were randomized into two groups

Pre-assignment

Screening details:

The prerequisites for inclusion were age > 18 and presence of a sinus rhythm. Exclusion criteria: history of coronary stent placement, coronary bypass graft surgery or heart transplantation, history of multiple myeloma, impaired renal function (eGFR < 60 ml/min), untreated hyperthyreosis, as well as a history of allergic reaction to contrast media

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	iodixanol

Arm description:

Patients referred to udnergo Cardiac CT were randomized and underwent the indicated Cardiac CT during the intravenous application of iodixanol

Arm type	Active comparator
Investigational medicinal product name	Iodixanol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Patients within both groups were subdivided according to their body weight into three body weight groups (<55 kg, 55 – 100 kg, >100 kg). Based on weight, the total amount of iodine was defined for each group, which determined the other parameters for contrast injection. The acquisition time, the injection duration, and thus, the injection speed, were defined, ensuring the same iodine delivery rate within every body weight class for both contrast agents (see Table 1). Patients who weighed below 55 kg received an iodine dose of 28 g, with a delivery rate of 1.76 g per second, patients between 55 kg and 100 kg received a total dose of 32 g, with a flow of 2 g per second, and patients above 100 kg received 36 g at a rate of 2.24 g per second.

Arm title	iomeprol

Arm description:

Patients referred for Cardiac CT were randoimzed and underwent the indicated examination during the intravenous administration of iomperol in this arm

Arm type	Active comparator
Investigational medicinal product name	iomeprol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients within both groups were subdivided according to their body weight into three body weight groups (<55 kg, 55 – 100 kg, >100 kg). Based on weight, the total amount of iodine was defined for

each group, which determined the other parameters for contrast injection. The acquisition time, the injection duration, and thus, the injection speed, were defined, ensuring the same iodine delivery rate within every body weight class for both contrast agents (see Table 1). Patients who weighed below 55 kg received an iodine dose of 28 g, with a delivery rate of 1.76 g per second, patients between 55 kg and 100 kg received a total dose of 32 g, with a flow of 2 g per second, and patients above 100 kg received 36 g at a rate of 2.24 g per second.

Number of subjects in period 1	iodixanol	iomeprol
Started	146	153
Completed	146	153

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	299	299	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	220	220	
From 65-84 years	77	77	
85 years and over	2	2	
Adults (18 - 64)	0	0	
Gender categorical Units: Subjects			
Female	138	138	
Male	161	161	

End points

End points reporting groups

Reporting group title	iodixanol
Reporting group description:	
Patients referred to udnergo Cardiac CT were randomized and underwent the indicated Cardiac CT during the intravenous application of iodixanol	
Reporting group title	iomeprol
Reporting group description:	
Patients referred for Cardiac CT were randoimzed and underwent the indicated examination during the intravenous administration of iomperol in this arm	

Primary: heart rate variation

End point title	heart rate variation
End point description:	
heart rate variation: heart rate should be assessed at different time points (see also tabe 2) to allow for calculation of the heart rate variation: baseline: heart rate 1 minute after Ca-scoring is defined as baseline heart rate (1 minute after Ca scoring, heart beats are counted for a time period of 30 seconds and are divided by 30 and multiplied by 60. This leads to baseline mean heart rate) maximum/minimum heart rate: highest/lowest observed heart rate within 1 minute after start of contrast injection is defined as maximum/minimum heart rate mean heart rate: mean heart rate within 1 minute after start of contrast injection is defined as mean heart rate (after start of contrast injection, heart beats are counted for a time period of 60 seconds) heart rate variation: fluctuation from baseline is defined as heart rate variation (minimal and maximal heart rate during a time period of 1 minute are assessed and standard deviation from baseline is calculated)	
End point type	Primary
End point timeframe:	
60 sec after contrast injection	

End point values	iodixanol	iomeprol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	106		
Units: durance of heart beat in msec				
number (not applicable)	101	106		

Attachments (see zip file)	heart rate variation/Figure 3.tif

Statistical analyses

Statistical analysis title	heart rate variation
Statistical analysis description:	
The average heart rate (in bpm) of the initial measurement phase (60 seconds, before CA administration) was defined as the patient's resting heart rate (baseline). Heart rate changes after CA	

administration, defined as the deviations from the baseline, were determined once per second over a total of 50 seconds for each patient, and the two groups were then tested for significant differences.

Comparison groups	iodixanol v iomeprol
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	≤ 0.05
Method	Mann-Whitney U

Notes:

[1] - To evaluate changes in the variability of the RR interval duration during CA administration, two parameters were assessed: the standard deviation of all normal RR intervals (SDNN), which covers long-term RR variability; and the Root Mean Square of the Successive Differences (RMSSD), which covers short-term RR variability.

Secondary: arterial contrast enhancement:

End point title	arterial contrast enhancement:

End point description:

The arterial enhancement in predefined vascular segments will be measured by one experienced technician.

End point type	Secondary

End point timeframe:

on the CT images, after acquisition

End point values	iodixanol	iomeprol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	106		
Units: Hounsfield Units				
number (not applicable)	101	106		

Attachments (see zip file)	table 3: HU, CNR and SNR/Table 3.pdf

Statistical analyses

Statistical analysis title	arterial enhancement

Statistical analysis description:

The HU values gathered for the four anatomical regions (left atrium, left ventricle, sinus valsalvae, and left main), as well as the calculated values for SNR and CNR, were tested for significant differences among the two CA groups using an unpaired t-test.

Comparison groups	iodixanol v iomeprol
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	t-test, 1-sided

Secondary: overall image quality

End point title	overall image quality

End point description:

the overall subjective image quality will be assessed by two blinded readers in consensus according to the following five point scale:
0: not assessable
1: poor quality; more than 50% of segments not assessable
2: suboptimal quality, diagnosis hampered
3. good quality, diagnosis possible without major limitations
4. excellent quality; no limitations

End point type	Secondary

End point timeframe:

assessment after image acquisition

End point values	iodixanol	iomeprol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	106		
Units: quality core (Likert score)				
number (not applicable)	101	106		

Attachments (see zip file)	table 4 +5: image quality score/Table 4+5.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: pateint discomfort

End point title	pateint discomfort

End point description:

the patient discomfort will be assessed after the end of heart beat measurements using a standardized visual assessment score (VAS, 0-10). Feeling of heat, cold, and pain at the injection site ranging from 0 = no pain to 10 = very severe pain will be assessed (attachement 1).

End point type	Secondary

End point timeframe:

after image acquisition

End point values	iodixanol	iomeprol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	106		
Units: VAE	101	106		

Attachments (see zip file)	figure 5 heat sensation/Figure 5.tif

Statistical analyses

No statistical analyses for this end point

Secondary: safety / AE

End point title	safety / AE

End point description:

adverse events will be assessed up to 30 minutes after start of the contrast injection

End point type	Secondary

End point timeframe:

0 - 30' after CT acquisition

End point values	iodixanol	iomeprol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	153		
Units: AE	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 0 - 30' after CT image acquisition similar as the normal clinical care	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22

Reporting groups	
Reporting group title	iodixanol
Reporting group description: including all patients receiveing iodixanol as the contrast agent according to the randomization	
Reporting group title	iomeprol
Reporting group description: including all patients receiveing iomeprol as the contrast agent according to the randomization	

Serious adverse events	iodixanol	iomeprol	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 146 (0.00%)	0 / 153 (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: 3 %

Non-serious adverse events	iodixanol	iomeprol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 146 (0.68%)	2 / 153 (1.31%)	
Immune system disorders			
mild allergic contrast media reaction			
subjects affected / exposed	1 / 146 (0.68%)	2 / 153 (1.31%)	
occurrences (all)	1	2	

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