Iodixanol versus Iopromide at coronary CT angiography: lumen opacification and effect on heart rhythm - the randomized IsoCOR trial

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ABSTRACT

Purpose: Demonstrate that using contemporary cardiac CT protocols equal coronary lumen opacification can be achieved with iso-osmolar and low-osmolar contrast media, when injected at the same iodine delivery rate. In addition, we investigate the cardiovascular effect of iso-osmolar contrast media, and achieved image quality.

Materials and Methods: Institutional review board approval was obtained. Written informed consent was obtained from all subjects. Between November 2015 and August 2016 306 patients (167 (55%) women) at least 18 years old and weight between 50-125kg, were prospectively randomized between iso-osmolar iodixanol-270 (Visipaque) and low-osmolar iopromide-300 (Ultravist). All coronary segments were assessed for intraluminal opacification and image quality and compared using a student T-test. Heart rate, arrhythmia, patients discomfort and adverse events were also monitored.

Results: Measured coronary attenuation values were comparable between both contrast media (469 ± 167 HU vs 447 ± 166 HU, p=0.241, 95% CI: -15.1 -60.0), including subanalyses. Adjusted for the lower iodine concentration, the mean iodixanol-270 bolus was higher compared to iopromide-300 (76.8 ± 11.6 ml vs. 69.7 ± 10.8 ml, p<0.001). The higher injection rate was associated with a higher pressure (111 ± 44 PSI vs 90 ± 36 PSI, p<0.001). Although in the iodixanol-270 group patients experiences less heat discomfort (72% vs. 86% p<0.001), no differences in heart rate or rhythm were observed.

Conclusion: If injected at comparable iodine delivery rates, the iso-osmolar contrast medium iodixanol-270 is not inferior to low-osmolar contrast medium iopromide-300 in terms of coronary opacification (body weight 50-125 kg). Iodixanol-270 was associated with less heat discomfort, but did not affect heart rate differently compared to iopromide-300.

INTRODUCTION

Coronary computed tomography angiography (CTA) is an established test in the diagnostic work up of patients with stable angina pectoris and allows for reliable exclusion of coronary artery disease (1). As a result of continued scanner development and iterative reconstruction algorithms contemporary CT systems allow for coronary imaging at lower tube voltages (kV). Nowadays many patients can be scanned using 80kV, lowering overall radiation exposure. Because of greater photoelectric effect and decreased Compton scattering, imaging at a lower kV also increases the attenuation differences between iodine and soft tissue (2). Because current technology allows comparable opacification at lower intra-coronary iodine concentrations, the iodine delivery rate can be reduced, permitting application of contrast media with lower iodine concentrations. When osmolality increases, the viscosity as well as opacification of the contrast agent increases but the tolerance power of the patients decreases. Sensations of heat, discomfort or even pain are directly related to the osmolality of the contrast medium(3).

Most roentgen contrast media have an osmolarity higher than blood plasma, which is responsible for various clinical effects, such as sensations of heat, discomfort and even pain(4). Invasive coronary angiography studies suggest that arrhythmia occur more frequently with low-osmolar contrast media. Iso-osmolar contrast agents, with an osmolarity equal to plasma, cause less heart rate acceleration and arrhythmia, which should be of potential benefit for CT image quality (3, 5-8). In terms of opacification and image quality comparisons between iso-osmolar and low-osmolar contrast media have demonstrated mixed results (6, 9, 10). Because many studies compared protocols of identical injection rates of contrast media, but unequal iodine concentrations, observations may be affected by differences in the net iodine delivery rates(3, 5-12). It remains unclear how an iso-osmolar contrast medium affects the opacification of the coronary arteries when identical iodine fluxes are applied. Also the effect on heart rate, arrhythmia, and subsequent image quality in case of identical iodine fluxes has not yet been evaluated in a randomized trial.

The aim of the Isocor randomized-controlled trial was to demonstrate that using contemporary cardiac CT protocols equal coronary lumen opacification can be achieved with iso-osmolar and low-osmolar contrast media, when injected at the same iodine delivery rate. In addition, we investigate the cardiovascular effect of iso-osmolar contrast media, and achieved image quality.

MATERIALS AND METHODS

Study Design

The Isocor trial is a non-inferiority, multicentre, double-blinded randomized-diagnostic validation trial comparing the opacification between an iso-osmolar (iodixanol) and a low-osmolar (iopromide) contrast medium. Patients referred for coronary CTA were prospectively enrolled at three hospitals in Rotterdam. The study was conducted in accordance with the Declaration of Helsinki and international standards of Good Clinical Practice and was approved by the medical ethics committees of the central coordinating centre and both participating sites. Written informed consent was obtained from each participating patient. The Isocor trial is registered at the EU Clinical trials register (www.clinicaltrialsregister.eu), EUdract-number 2014-000681-22. GE Healthcare, the manufacturer of iodixanol, provided unrestricted financial and material support (iodixanol contrast medium). The authors had full control of the data and information submitted for publication.

Study participants

Patients aged 18 years or older, body weight between 50-125kg, and referred for coronary CT-angiography in the context of suspected coronary artery disease (CAD) were study eligible. Exclusion criteria were pregnancy, renal dysfunction (eGFR<45ml/min/1.73m^2), allergies to iodine contrast media, manifest thyrotoxicosis, arrhythmia including atrial fibrillation/flutter, 2nd or 3rd degree atrioventricular block, frequent ectopic beats prior to the exam (discretion of referrer), prior coronary artery bypass graft surgery or percutaneous coronary intervention with stents.

Randomization and blinding

From an electronically created randomization list, allocation results were placed in numbered envelopes, which were opened just prior to the CT scan when an eligible patient consented to the study. The allocation was unknown to the patient and to the reader of the images. For practical reasons (different injection rates) the CT technicians performing the examination were not blinded with regard to allocation.

Contrast material and injection

Iodixanol-270 mg iodine per ml (Visipaque, GE Healthcare, Amersham, UK) and iopromide-300 mg iodine per ml (Ultravist, Bayer Healthcare, Berlin, Germany) were stored and administered in a similar, clinically standard manner, in accordance with the summary of product characteristics (SPC). Bottles of contrast media were stored at the CT suite at 37° Celsius. Using a disposable system, contrast medium was transferred to a dual-head power injector, with external heating element. The power injector was then connected

to an 18-gauge IV canula in the antecubital vein. All participating hospitals used the same contrast injector type (Medrad® Stellant® CT Injection System, Bayer Medical Care Inc., Indianola, PA, USA). Contrast media were injected to achieve a net iodine delivery rate of 1.5gI/s (bodyweight 50-100kg), or 1.75gI/s for larger patients (bodyweight 100-125kg) to maintain sufficient concentrations of iodine in the bloodstream and the coronary arteries at higher anticipated cardiac output. Iodixanol-270 was injected at 5.6ml/s (body weight 50-100kg) or 6.5ml/s (100-125kg), iopromide-300 was injected at 5.0ml/s (50-100kg) or 5.8ml/s (100-125kg). The total contrast volume was calculated by [estimated scan duration + 8 seconds] * [flow rate], followed by a 40cc saline bolus chaser at same flow rate. The pressure limit of the power injector was 325 PSI.

CT examination

All CT angiograms were performed by standard contemporary protocols using 2nd or 3rd generation dual-source CT systems (Somatom Definition Flash and SOMATOM Force, Siemens Healthineers, Forchheim, Germany). If indicated (heart rate >65 bpm) and clinically tolerable, beta-blockers were administrated. All patients received sublingual nitroglycerin just before scanning. First a non-enhanced calcium scan was performed to measure the Agatston score. The median total Agatston calcium score was 4 [0;89]. The scan parameters are summarized in table 2. In both groups the majority was imaged using the prospectively ECG-triggered axial scan mode (92% vs 94%, p=0.473), with an exposure window during diastole and/or systole depending on the heart rate. . Automatic tube current modulation and tube voltage selection based on the scout images were employed. The tube settings were optimized to achieve sufficient signal to noise. The system automatically selected the lowest possible *tube* voltage that still be supported by the tube current in a given patient and application, in order to achieve sufficient image quality at the lowest possible dose. The tube current was 70 or 80kV in 51% of patients in the iodixanol-270 group and 53% in the iopromide-300 group (table 2). The dose-length-product (DLP) and effective dose (k=0.017) was 160±119Gycm and 2.7±2.0mSv in the iodixanol group, and 174±160mGycm and 3.0±2.7msV (p=0.387) in the iopromide group. Iterative reconstruction (Strength-3) was used. The reconstructed slice thickness was 0.6mm, reconstruction increment 0.4mm, reconstructed area dimensions 180x180mm.

Image evaluation

All CTA images were assessed by an independent, experienced reader (ML, 4 years of cardiac CT experience), blinded to the patients' clinical characteristics and the contrast medium used. The mean attenuation (Hounsfield units,HU) and standard deviation were measured in the proximal, mid and distal part of the right coronary artery (RCA), left anterior descending artery (LAD) (13), and left circumflex artery (LCX). The attenuation

measurements were performed on the axial images in vessel segments with a minimal diameter of 2mm and good or diagnostic image quality, by placing a circular region-of-interest (ROI) with a minimum number of 10 image elements (pixels) in the center of the vessel at a location of sufficient image quality. Attenuation was also measured in the middle of the atrial and ventricular cavities, the middle of the ventricular septum (myocardium) and the ascending and descending aorta. For each coronary segment subjective image quality was classified on a 3-point scale as good, diagnostic, or poor. Image noise, signal-to-noise ratio, and contrast-to-noise ratio were determined for all scans (see formulas). The image noise was derived from the averaged SDs of the CT attenuation values sampled using two large regions of interest in the proximal segments of both the left and right coronary arteries. The signal intensity was defined as the mean attenuation values derived from the same 2 regions of interest. The signal-to-noise ratio was calculated as mean CT attenuation values of the left and right coronary arteries divided by image noise. The contrast-to-noise ratio was defined as the difference between the mean CT attenuation values of the proximal coronary arteries and the mean density of the left ventricular wall, which was divided by image noise.

$$Contrast-to-noise\ ratio = \frac{([attenuation]LCA + [attenuation]RCA\ /2) - [attenuation]LV\ wall}{[attenuation\_SD]LCA + [attenuation\_SD]RCA\ /2}$$

Clinical effects and safety

The cardiovascular response to the contrast injection was monitored by measuring the mean heart rate. The heart rate was measured over 15 seconds before scanning (free breathing), at the time of the calcium scan (without contrast injection, but breath holding), and during CTA (after contrast injection and with breath holding), calculated from the ECG traces during data acquisition. Also the number of ectopic beats on the ECG recordings during CT-angiography were recorded, as well as the occurrence of atrial fibrillation. All adverse events, such as contrast extravasation, severe arrhythmia with hemodynamically significance, allergic reactions and renal failure were reported. The physical complaints during contrast injection were evaluated using a 5-point scale ranging from 0(no complaints) to 4(worst thinkable).

Outcomes

The primary outcome was the coronary lumen opacification, defined as the averaged attenuation values (Hounsfield Units, HU) sampled in the middle segment of the LAD, the middle segment of the RCA, and proximal segment of the LCX, demonstrating non-inferiority. Secondary outcome measures of image quality were the contrast attenuation values in the proximal, middle and distal coronary arteries, respectively, the signal-to-noise ratio (SNR), the contrast-to-noise ratio (CNR), and the scaled subjective image

quality per coronary segment. Clinical outcome measures included adverse events, heart rate, arrhythmia, and patient reported sensations.

Statistical analyses

For 80%-power at a one-sided p-value of 0.025 we needed to recruit at least 272 patients to detect a difference of 30HU in coronary opacification, which was pre-specified and considered relevant for image interpretation. Anticipating a drop-out of up to 10%, we aimed to recruit 300 patients.

The primary endpoint to assess coronary opacification, the sampled and averaged attenuation values in the mid-segment of the RCA and LAD and proximal Cx, is a continuous variable with normal distribution reported as means ±SD. The hypothesis would be rejected if coronary opacification by iodixanol-270 were >30HU lower than by iopromide-300. Non-inferiority can be concluded when the lower bound of the confidence interval of the difference in attenuation does not exceed the non-inferiority margin(-Δ) of -30HU. Unavailable or technically failed scans were excluded. To meet the intention-to-treat principle, we corrected for missing data due to poor image quality. Missing values were replaced by the lowest measured mean coronary opacification (142HU). Results between the groups were compared using a student t-test. To correct for potential confounders influencing the opacification we also performed an analysis of covariance (ANCOVA).

Secondary, continuous measures (attenuation measures, SNR, CNR, contrast injection parameters) and categorical parameters (subjective quality, artifacts, adverse events) were compared using the student-t and Chi-square tests. The heart rate and change in heart rate in patients were compared using Wilcoxon signed-ranks test. Data distribution was tested with the Shapiro-Wilk test. Multi-variable linear regression analysis was performed to assess potentially confounding parameters towards the vessel opacification, which were pre-specified and included age, gender, height, weight, BMI, heart rate, left ventricular function (determined by cardiac echocardiography, registered from patient records if available), IV gauge location, as well as other covariates found to be different between the randomization groups (gender and systolic blood pressure). To test whether injection rate was an effect modifier of contrast agent on opacification an ANCOVA model was performed with the interaction term contrast injection rate x randomization. A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 21, IBM Corp, Armonk NY, USA), according to the intention-to-treat principle.

RESULTS

Study population

Between November 2015 and August 2016 329 eligible patients were approached, of whom 9(3%) declined participation, 4(1%) had atrial fibrillation, 3(1%) had a known contrast allergy, 2(1%) were unable to consent, 2(1%) had a body weight >125kg, 2(1%) were excluded because of technical reasons, and 1(0.3%) was excluded because of renal dysfunction (figure 1). Of the 306 enrolled patients, 154(50%) were randomly assigned to iodixanol-270 and 152(50%) to iopromide-300. No scans were excluded because of overall non-diagnostic image quality. All patients were included in the intention-to-treat analysis (figure 1). The mean age was 56±12 years. There were more women randomized to iopromide-300 (61% vs 48%, p=0.022), and also the mean systolic blood pressure was higher in this group (143±21 mmHg vs 136±20 mmHg, p=0.008). Otherwise there were no significant differences in clinical symptoms and cardiovascular risk factors (table 1). Most patients presented with chest pain complaints (90% vs 89%, p=0.896).

Table 1. Patient characteristics

	Iodixanol-270 (n=154)	Iopromide-300 (n=152)
Mean age (years)	56±12	56±11
Female sex	74 (48%)*	93 (61%)*
Systolic blood pressure (mmHg)	136±20*	143±21*
Diastolic blood pressure (mmHg)	82±11	82±12
Length (cm)	172±11	172±10
Weight (kg)	82±15	81±16
Body-mass index (kg/m^2)	27±4	27±5
eGFR (ml/min/1.73m^2)	76±16	75±16
Cardiovascular risk factors		
Current/past smoker	34 (22%)	22 (14%)
Hypertension	49 (32%)	49 (32%)
Dyslipidaemia	39 (25%)	36 (24%)
Diabetes mellitus	16 (10%)	14 (9%)
Family history of ischemic heart disease	33 (21%)	39 (26%)
History of obesity (BMI ≥30kg/m^2)	45 (30%)	37 (25%)

Patient characteristics presented as mean ± standard deviation or n (%), or median and interquartile range. Hypertension: >150 systolic or >90 diastolic mmHg or using tension-lowering medication. Dyslipidaemia: total cholesterol >5mmol/L, low-density lipoprotein >3mmol/L, or on lipid-lowering medication. Diabetes Mellitus: plasma glucose >11.0mmol/L, or treated with diet regulation or medication. * Significant difference (p<0.05).

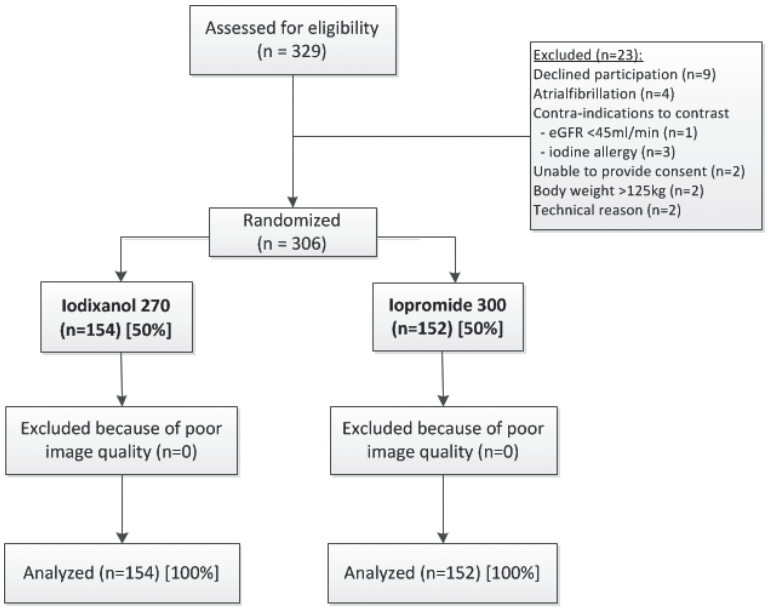

Figure 1. Enrolment and randomization of patients. There were no patients with a poor image quality of all the coronary arteries, so no scans were excluded based on poor image quality.

Quantitative and qualitative image quality

The primary endpoint coronary lumen opacification, averaged in the middle segment of the RCA, LAD and proximal LCx, was 469 ± 167 using iodixanol-270 and 447±_166 using iopromide-300 (p=0.241)(95% CI: -15.1 – 60.0) (appendix 1). Corrected for potential confounders (age, gender, BMI and injection rate) the mean coronary lumen opacification in the iodixanol-270 group was 471 ± 450, compared to 439 ± 417 in the iopromide-300 group (p=0.037, 95% CI: 1.9 – 62.7). Comparisons on a segmental level, summarized for proximal, middle and distal coronary segments, and averaged per patient showed no differences (iodixanol-270 462±155 HU vs iopromide-300 440±150 HU, p=0.220). Interestingly, attenuation values in the interventricular septum were higher in the iopromide-300 group (110±29 vs 117±33, p=0.034). Coronary opacification was positively influenced by female gender (55.9 HU higher in women; 95% CI 12.0,100.0; p=0.013). Opacification was positively affected by age (4.0 HU increase per year of age; 95% CI 2.0,5.9; p<0.001). Opacification was negatively influenced by BMI (-20.6 HU per 1kg/m^2; 95% CI -24.8,-16.5, p<0.001), weight (-6.3 HU per kg; 95% CI -7.2,-5.5, p<0.001) and length (B -4.6 lower per cm; 95% CI -6.2,-2.9, p<0.001). LV function, systolic blood pressure, heart rate before and during contrast administration and the location of the IV canula did not affect mean attenuation values. In a multivariate analysis the remaining predictor of coronary opacification was age (+3.1 HU per year; 95% CI 0.05,6.19, p=0.046). There were no differences in attenuation between both contrast media through the

sequential vasculature from right atrium to the distal aorta (appendix 2). The effect of contrast agent on opacification was not depended on the injection rate (p=0.652). A case example of the coronary opacification with both contrast agents is shown in figure 2. The signal-to-noise ratio and contrast-to-noise ratio did not differ between the groups (SNR: iodixanol-270: 22.3±9.3 HU vs 23.5±10.9 HU, p=0.290)(CNR: iodixanol-270: 17.2±7.7 HU vs 17.5±8.4 HU, p=0.729) (appendix 1). The subjectively assessed image quality was good in 86% and 85% of all coronary segments and did not differ between iodixanol-270 and iopromide-300 (p=0.283, appendix 3).

Concordant with the different iodine concentrations the contrast volume was higher in the iodixanol-270 group to achieve similar iodine delivery rates (mgI/sec) to the iopromide-300 group (76.8±11.6 ml vs 69.7±10.8 ml, p<0.001), and at higher injection pressures (111±44 PSI vs 90±36 PSI, p<0.001)(table 2).

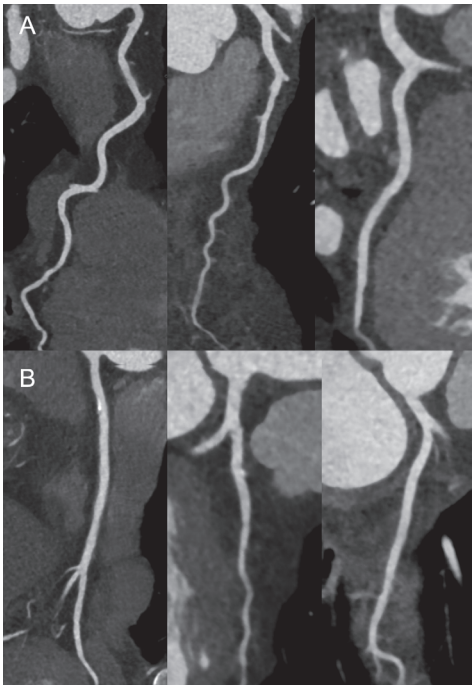

Figure 2. Coronary lumen opacification performed with both contrast agents. Both patients were men of 54 years old and a BMI of 25. Patient A was scanned with iodixanol-270, at a heartrate of 63bpm and had a calciumscore of 0. Patient B was scanned with iopromide-300 at heartrate 56bpm and had a calciumscore of 68. From left to right the right coronary artery (RCA), left anterior descending artery (LAD) and left circumflex artery (LCx) are shown.

Effect on heart rhythm

Beta-blockers were administrated in nearly half of the patients. For both groups combined, the heart rate decreased during the breath-held calcium scan from 64.8±9.9 bpm to 63.4±10.5 bpm (p<0.001). During contrast-enhanced CT-angiography the heart rate remained virtually unchanged in the iodixanol-270 (+0.01±4.56, p=0.986) and the iopromide-300 group (+0.32±5.37; p=0.473), without a difference between both groups

(p=0.588) (figure 3). Ectopic beats occurred in 3(2%) of iodixanol-270 patients, compared to 6(4%) of iopromide-300 patients (p=0.334). No atrial fibrillation occurred in either group before or after contrast injection.

Table 2. Scan characteristics

	Iodixanol-270 (n=154)	Iopromide-300 (n=152)	p-value
Heart rate			
Before scanning (bpm) (mean±SD) [range]	65 ± 9 [45-98]	65 ± 11 [44-115]	0.638
During calcium scan (bpm) (mean±SD) [range]	63 ± 10 [45;98]	63 ± 11 [46-118]	0.887
During CTA(bpm) (mean±SD) [range]	63 ± 11 [43-98]	64 ± 11 [42-114]	0.590
Heart rate change* (bpm) (mean±SD)	0.01 ± 4.56	0.32 ± 5.37	0.588
Ectopic beats during and after contrast injection	3 (2%)	6 (4%)	0.334
Occurrence of atrial fibrillation	0	0	1.000
Pre medication			
B-blockers	70 (46%)	65 (43%)	0.646
Contrast injection			
Contrast bolus (cc) (mean±SD) [range]	76.8 ± 11.6 [48-100]	69.7 ± 10.8 [45-95]	<0.001
Iodine delivery rate, patients 50-100kg (gI/s)	1.5	1.5	
Iodine delivery rate, patients 100-125kg (gI/s)	1.75	1.75	
Maximal injection pressure (PSI)	111 ± 44	90 ± 36	<0.001
Scanning technique			0.473
Retrospectively gated spiral scan mode	13 (8%)	9 (6%)	
Prospectively triggered axial scan mode	117 (76%)	124 (82%)	
Prospectively triggered high-pitch spiral scan mode	24 (16%)	19 (13%)	
Tube current (mAs) (mean±SD) [range]	341 ± 103 [88-600]	345 ± 103 [108-568]	0.716
Tube voltage (kV) (median, IQR)	80 (80;100)	80 (80;100)	0.796
Scan time (seconds) (mean±SD)	4.6 ± 2.4	4.9±2.3	0.264
Radiation dose			
Dose-length product (mGycm) (mean±SD) [range]	160 ± 119 [19;561]	174 ± 160 [25;1038]	0.387
Total calcium score (mean±SD) [range]	118 ± 348 [0;3429]	123 ± 308 [0;2765]	0.897

Patient characteristics presented as mean ± standard deviation and range, or n (%), or median and interquartile range. The heart rate before scanning was a mean over 15 seconds. *Difference in heart rate recorded during the calcium scan and the contrast-enhanced CTA. Number of patients with ectopic beats throughout the ECG recording during and after contrast injection. B-blockers are oral and intravenous. The maximum contrast injection pressure measured in pound-force per square inch (PSI). Dose-length product (DLP) in mGycm for CT-angiography.

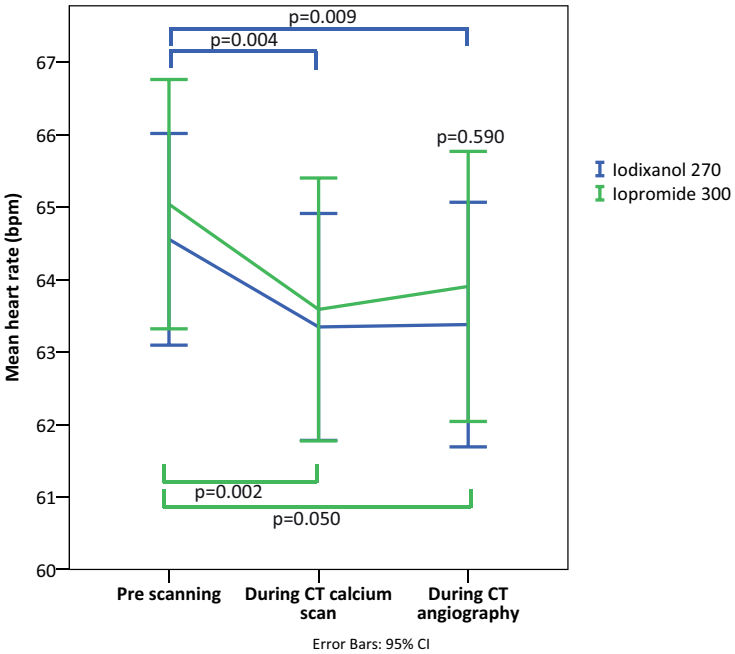

Figure 3. Change in heart rate. The mean heartrate (beats per minute), before the CT exam, calcium scan, and CT-angiography. Compared to measurements before the CT scan, heart rates decreased during both the calcium scan (iodixanol-270: p=0.004, iopromide-300: p=0.002) and CT-angiography (iodixanol-270: p=0.009, iopromide-300: p=0.050). The heart rate during CT angiography was not significantly different between the iodixanol-270 and iopromide-300 group (p=0.590).

Clinical effect and safety

In the iodixanol-270 group fewer patients experienced heat discomfort during the scan compared to iopromide-300 group (72% vs 86%, p<0.001)(figure 4). Other symptoms and sensations were observed in similarly low rates between both groups. One patient in the iodixanol-270 group experienced contrast extravasation. In the iopromide-300 group two patients experienced mild allergic reactions (sneezing and urticaria, respectively), and one experienced blurred vision <2hours after the scan, all of which resolved shortly without treatment. No arrhythmias or renal failure occurred.

DISCUSSION

This multicentre, randomized trial was designed to assess whether iso-osmolar contrast medium with a low iodine concentration provides comparable coronary opacification to low-osmolar contrast media, if injected at a similar iodine delivery rate. We found that 1) coronary lumen opacification by iso-osmolar contrast (iodixanol) is not inferior

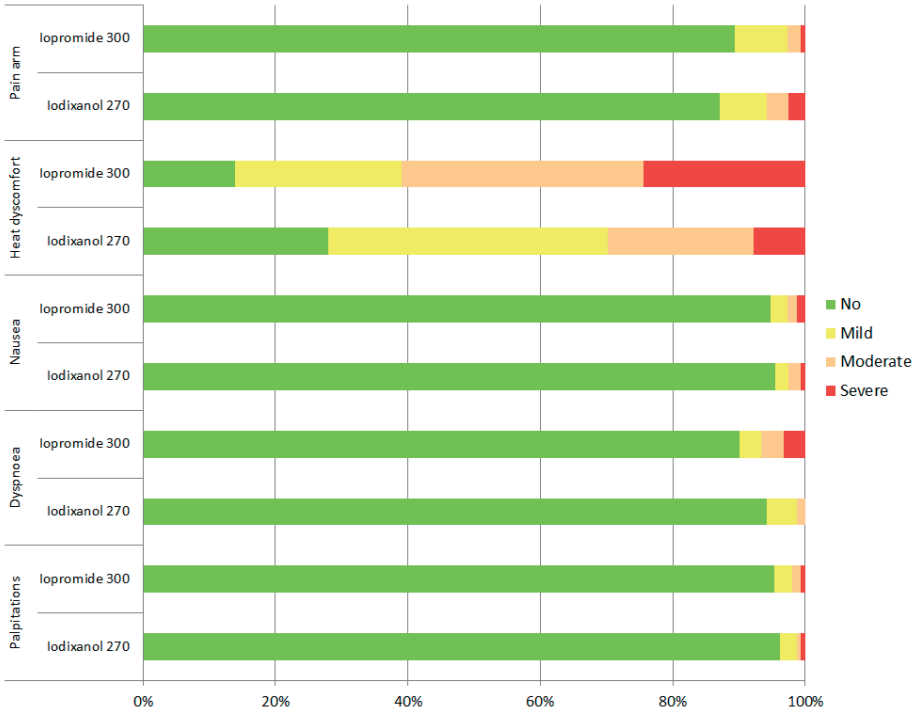

Figure 4. Clinical effect. All symptoms were classified as no symptoms, mild, moderate or severe. The iodixanol-270 group experienced less heat discomfort during contrast administration compared to the iopromide-300 group (72% vs 86%, p<0.001). There were no significant differences in other symptoms and sensations between both groups.

to a low-osmolar contrast (iopromide), 2) while iopromide-300 was associated with more frequent heat sensations, heart rate was not affected differently between the two groups, 3) objective and subjective measures of image quality were similar between iodixanol-270 and iopromide-300.

In this study we found that if contrast media are injected at comparable iodine delivery rates, by injecting the iso-osmolar contrast medium at a higher injection rate, coronary opacification by iodixanol-270 is not inferior to iopromide-300. In terms of coronary arterial opacification and image quality comparisons between iso-osmolar and low-osmolar contrast media have demonstrated mixed results. While some studies demonstrated comparable coronary opacification between iso-osmolar and low-osmolar contrast (6, 9), there is also data showing significantly lower opacification of low-osmolar contrast compared to high iodine-osmolality (5, 10). However, in these trials contrast media were injected with unequal iodine delivery rates.

Using an iodine delivery rate of 1.5 gI/s in both arms (body weight <100kg), we measured average attenuation values well above 400HU, with acceptable noise and image

quality. The injection rate of iodixanol-270 was 5.6 - 6.5 ml/s. Until recently achieving sufficient coronary opacification at reasonable contrast injection rates required contrast media with a high iodine concentration of up to 400mgI/ml. High attenuation values partially compensated for some of the limitations of cardiac CT related to residual motion and calcifications. Technological innovation, in particular improved temporal resolution and iterative image reconstruction techniques, allow for reliable coronary assessment at a lower coronary opacification. In addition, desired attenuation values can be achieved with lower intra-coronary iodine concentration by using more powerful roentgen tubes operated at lower tube voltages. Iterative reconstruction algorithms reduce image noise and improve SNR and CNR while keeping intravascular attenuation values homogenous (2, 14).

The osmolarity of contrast media is associated with several clinical effects, such as sensations of heat, discomfort and pain. Low-osmolar contrast media may increase heart rate, and thereby reduce image quality in coronary CT angiography. In the Isocor trial we found that the mean heart rate did not increase in either group. Multiple studies in stable patients evaluating suspected coronary artery disease, suggest that iso-osmolar contrast media cause less heart rate acceleration and arrhythmia (5, 7, 11, 15). Low heart rate and absent arrhythmia positively affect image quality in ECG-synchronized CT-angiography. However, other studies that compared iso-osmolar and low-osmolar contrast media in abdominal CT reported no difference in heart rate (12, 16). It should be noted that nearly half of the patients in this study received additional beta-blockers prior to scanning, but at comparable proportion in both groups.

In the Isocor study we found no significant differences in terms of coronary opacification, nor for several other objective parameters of image quality. Previously, some investigators demonstrated similar diagnostic accuracy, coronary attenuation and subjective image quality of CTA using either iso-osmolar or low-osmolar contrast (6, 9), while other studies demonstrated better coronary enhancement and fewer inadequately visualized segments using high-iodine concentration low-osmolar contrast protocols (5).

There were a few occurrences of contrast extravasation and mild allergy, and a single incidence of blurred vision, which is a known side-effect of both contrast agents. Maximal injection pressure was higher for iodixanol (PSI 111 ± 44) compared to iopromide (PSI 90 ± 36, <0.001) as a result of higher injection rates and higher viscosity (6.3cP vs 4.9cP at 37°C) for iodixanol, but never exceeded the safety threshold (PSI 325).

There are limitations to the study that require consideration. Because of the different injection rates the CT technicians could not be blinded towards the study allocation. However, this should not have affected the independent, blinded reading and establishment of the primary outcome. Although unlikely given the comparable image quality parameters, we cannot exclude differences in diagnostic accuracy related to the contrast media. Except for heart rate no other hemodynamic parameters were monitored. A sys-

tematic assessment of renal function after contrast exposure was not performed, however, no differences in CIN risk between iodixanol-270 and iopromide-300 have been reported in the past (19, 20). Comparison between the iso-osmolar contrast medium iodixanol was compared to only a single low-osmolar contrast medium, which may not be representative for the entire class.

In conclusion, if injected at comparable iodine delivery rates, the iso-osmolar contrast medium iodixanol-270 is not inferior to low-osmolar contrast medium iopromide-300 in terms of coronary opacification (body weight 50-125 kg). Iodixanol-270 was associated with less warmth discomfort during contrast injection, but did not affect heart rate or image quality compared to iopromide-300.

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