Comparative effectiveness of initial computed tomography and invasive coronary angiography in women and men with stable chest pain and suspected coronary artery disease: multicentre randomised trial

DISCHARGE Trial Group

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ABSTRACT

OBJECTIVE

To assess the comparative effectiveness of computed tomography and invasive coronary angiography in women and men with stable chest pain suspected to be caused by coronary artery disease.

DESIGN

Prospective, multicentre, randomised pragmatic trial.

SETTING

Hospitals at 26 sites in 16 European countries.

PARTICIPANTS

2002 (56.2%) women and 1559 (43.8%) men (total of 3561 patients) with suspected coronary artery disease referred for invasive coronary angiography on the basis of stable chest pain and a pre-test probability of obstructive coronary artery disease of 10-60%.

INTERVENTION

Both women and men were randomised 1:1 (with stratification by gender and centre) to a strategy of either computed tomography or invasive coronary angiography as the initial diagnostic test (1019 and 983 women, and 789 and 770 men, respectively), and an intention-to-treat analysis was performed. Randomised allocation could not be blinded, but outcomes were assessed by investigators blinded to randomisation group.

MAIN OUTCOME MEASURES

The primary endpoint was major adverse cardiovascular events (MACE; cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). Key secondary endpoints were an expanded MACE composite (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack, or major procedure related complication) and major procedure related complications.

RESULTS

Follow-up at a median of 3.5 years was available in 98.9% (1979/2002) of women and in 99.0% (1544/1559) of men. No statistically significant gender interaction was found for MACE (P=0.29), the expanded MACE composite (P=0.45), or major procedure related complications (P=0.11). In both genders, the rate of MACE did not differ between the computed tomography and invasive coronary angiography groups. In men, the expanded MACE composite endpoint occurred less frequently in the computed tomography group than in the invasive coronary angiography group (22 (2.8%) *v* 41 (5.3%); hazard ratio 0.52, 95% confidence interval 0.31 to 0.87). In women, the risk of having a major procedure related complication was lower in the computed tomography group than in the invasive coronary angiography group (3 (0.3%) *v* 21 (2.1%); hazard ratio 0.14, 0.04 to 0.46).

CONCLUSION

This study found no evidence for a difference between women and men in the benefit of using computed tomography rather than invasive coronary angiography as the initial diagnostic test for the management of stable chest pain in patients with an intermediate pre-test probability of coronary artery disease. An initial computed tomography scan was associated with fewer major procedure related complications in women and a lower frequency of the expanded MACE composite in men.

TRIAL REGISTRATION

NCT02400229ClinicalTrials.gov NCT02400229.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Compared with men, women presenting with chest pain have more symptoms but less severe myocardial ischaemia and less extensive epicardial coronary artery disease

Computed tomography (CT) can rule out obstructive coronary artery disease in patients with low to intermediate pre-test probability of CAD, but possibly less accurately in women than men

The comparative effectiveness of CT and invasive coronary angiography in the diagnosis and clinical management of CAD in women versus men in terms of clinical outcome is uncertain

WHAT THIS STUDY ADDS

The proportion of patients in whom obstructive CAD was found was similar with either a CT or ICA strategy, both in women (19.7% and 18.2%) and in men (33.5% and 35.3%)

In men, CT as the initial diagnostic test instead of initial ICA was associated with a lower risk of the expanded MACE composite (2.8% v 5.3%)

In women, initial CT was associated with a lower frequency of major procedure-related complications compared with initial ICA (0.3% v 2.1%)

Introduction

Studies consistently show that women presenting with stable chest pain and suspected coronary artery disease have more symptoms but less severe myocardial ischaemia and less extensive epicardial coronary artery disease compared with men.[1-4] This phenomenon has come to be known as the "gender paradox" and may lead to misdiagnosis and poorer outcome in women.[5-7] Importantly, in both women and men, coronary artery disease accounts for a similar and high proportion of all cause death in western

countries.[8-10] Nevertheless, the paucity of diagnostic and management trials specifically randomising either women or men and predefining such subgroups as targets for analysis in terms of outcomes precludes informed clinical recommendations.[11]

The reference standard for the diagnosis of obstructive coronary artery disease is invasive coronary angiography, which additionally allows coronary revascularisation to be done in the same session. However, rare but serious procedural complications can occur, and women undergoing invasive coronary examination and treatment may have a higher risk of bleeding, vascular complications, and stroke than men.[12-15]

Coronary computed tomography has been shown to be clinically useful for the non-invasive diagnosis of obstructive coronary artery disease in patients with stable chest pain and an intermediate pre-test probability because of a high diagnostic accuracy compared with invasive coronary angiography.[16-19] At the same time, computed tomography has been reported to have a comparable or slightly lower accuracy in women than in men, possibly owing to a reduced ability to detect stenosis in smaller coronary branches.[17 20 21] However, no large trials have assessed the gender specific comparative effectiveness of computed tomography and invasive coronary angiography as the initial test with regard to avoiding major procedure related complications and other key clinical outcomes.

In the DISCHARGE (Diagnostic Imaging Strategies for Patients With Stable Chest Pain and Intermediate Risk of Coronary Artery Disease) trial, women and men referred for invasive coronary angiography because of stable chest pain and an intermediate pre-test probability of coronary artery disease were allocated to initial computed tomography or initial invasive coronary angiography, with randomisation stratified for gender and centre.[22] For the total study population, the trial showed no significant difference between an initial computed tomography guided strategy and an initial invasive coronary angiography guided strategy with regard to the rates of major cardiovascular events (MACE) and found a lower frequency of major procedure related complications for an initial computed tomography strategy. The aim of this prespecified analysis of the DISCHARGE trial was to assess the gender specific comparative effectiveness of computed tomography and invasive coronary angiography.

Methods

Study design and patients

The study design, methods, and statistical analysis plan, including the prespecified gender related analysis of the DISCHARGE trial, have previously been published.[22 23] Briefly, DISCHARGE is an investigator initiated, pragmatic, assessor blinded, parallel group, randomised, multicentre study of the comparative effectiveness of computed tomography guided versus invasive coronary angiography guided management of patients with stable chest pain and a calculated intermediate pre-test probability of obstructive coronary artery disease clinically referred for invasive coronary angiography. The study was funded by the European Union (EU-FP7 Framework Programme) and was conducted at 26 clinical centres in 16 European countries (1 Austria, 1 Czech Republic, 1 Denmark, 1 Finland, 3 Germany, 1 Hungary, 1 Republic of Ireland, 2 Italy, 1 Latvia, 1 Lithuania, 2 Poland, 1 Portugal, 2 Romania, 2 Serbia, 2 Spain, and 4 UK), using standard operating procedures and strict quality control according to good clinical practice. Local or national ethics committees approved the study at each participating centre. The study was conducted and reported according to the CONSORT standards. The checklist is included in web appendix 1.[24]

Patients were eligible for the study if they were at least 30 years of age, were clinically referred for invasive coronary angiography because of stable chest pain with a calculated intermediate clinical pre-test probability (10-60%) of obstructive coronary artery disease,[17] and had no previous coronary revascularisation. The clinical referral for invasive coronary angiography because of suspected stable coronary artery disease was in accordance with the European Society of Cardiology guidelines at the time the study was conducted.[25-27] We collected self-reported gender information from all patients at baseline and did not biologically determine the sex of participants, following the Sex and Gender Equity in Research (SAGER) guidelines.[28] The terms "women" and "men" are used in this publication to acknowledge the absence of information on sex. Equal representation of both genders in the study population was intended, as the pre-test probability accounted for gender differences and randomisation was stratified by gender and centre. The exclusion criteria were haemodialysis, non-sinus rhythm, and pregnancy. All patients provided written informed consent. We estimated the pre-test probability of coronary artery disease after clinical referral of patients for invasive coronary angiography by using an automated calculation tool integrated into a web based system of electronic case report forms. The tool uses a model based on data from the Collaborative Meta-Analysis of Cardiac CT,[17] using patients' age, gender, and the type of stable chest pain.

Study procedures

Patients were randomly allocated to either initial computed tomography or initial invasive coronary angiography. We defined obstructive disease as detection of at least one ≥50% coronary artery luminal diameter stenosis. We categorised obstructive coronary artery disease as high risk anatomy if three vessel coronary artery disease, left main coronary artery stenosis, proximal left anterior descending coronary artery stenosis, or any combination of these was present. The clinical sites were provided with central management recommendations that incorporated contemporary European Society of Cardiology guidelines on the management of stable coronary artery disease in prevention of cardiovascular disease,

including the clinical indication for statins in clinical practice and on myocardial revascularisation,[25 26] as described in the study design and protocol.[23] The management decisions on patients were made by local heart team members and referring physicians on the basis of the computed tomography and invasive coronary angiography reports at each study site. Patients randomised to computed tomography as the initial test were subsequently managed according to the DISCHARGE computed tomography guided strategy protocol.[22] In both randomisation groups, patients without obstructive coronary artery disease by invasive coronary angiography or computed tomography were discharged back to the referring physician, and patients with obstructive coronary artery disease were managed according to guidelines.[25 27 29] Further recommendations included prescription of anti-anginal dugs, additional invasive or non-invasive functional testing, and coronary revascularisation as appropriate. Patients in both randomised groups were advised to be treated to target values for blood pressure, glycaemia, and lipids according to European guidelines on cardiovascular disease prevention.[26]

Computed tomography and invasive coronary angiography protocols

To ensure adherence to image quality criteria for computed tomography and invasive coronary angiography, we did a pilot study before the randomised study, in which each of the participating clinical centres had to provide imaging datasets of three patients for each imaging strategy. Adherence to the predefined standards for the computed tomography protocol and invasive coronary angiography recommendations were verified at all sites.[30]

At all clinical centres, trained personnel did computed tomography on at least 64 slice computed tomography scanners following a 10 step acquisition guide and scanner specific recommendations to identify coronary artery obstruction.[23] Trained interventional cardiologists did invasive coronary angiography at each participating centre according to contemporary guidelines and routine clinical practice at the individual clinical site.[29] Board certified and experienced radiologists with SCCT level II or III certification evaluated computed tomography.

Primary and secondary endpoints

The primary endpoint of this prespecified gender analysis was major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Cardiovascular death was diagnosed as defined by the Cardiac Safety Research Consortium, myocardial infarction was determined according to the third universal definition of myocardial infarction, and stroke was determined according to the updated definition for the 21st century as previously described.[22] Possible adverse cardiovascular events were collected in the electronic case report form, and events were adjudicated by independent assessors blinded to the study group assignment.

Key secondary endpoints included an expanded MACE composite (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack, or major procedure related complication occurring during or within 48 hours after computed tomography or invasive coronary angiography or related tests as prespecified in table 3 of the statistical analysis plan). Furthermore, the following additional composite endpoints were recorded: vascular death or myocardial infarction, cardiac death or myocardial infarction, all cause death, and myocardial infarction or stroke.

Major procedure related complications included death, non-fatal myocardial infarction, non-fatal stroke, further complications prolonging hospital admission by at least 24 hours, dissection (coronary, aortic), cardiogenic shock, cardiac tamponade, retroperitoneal bleeding, cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation), or cardiac arrest. Complications were classified according to the NCDR®CathPCI Registry®v4.4 Coder's Data Dictionary. The CONSORT extension for harms was adhered to.[31]

Randomisation and masking

Randomisation used a web based system (SecuTrial) to confirm eligibility criteria and record data for individual calculation of pre-test probability of disease. This web based system was used to randomly assign patients (1:1) to either computed tomography or invasive coronary angiography as the initial test. Block randomisation used computer generated and randomly permuted blocks with lengths of four, six, or eight stratified according to centre with central assignment. Randomisation of patients at each clinical centre was stratified according to gender. Patients and physicians could not be blinded to the study assignment.

Statistical analysis

The sample size estimation for the trial has been previously published[22]; it was based on the comparison of invasive coronary angiography versus computed tomography regarding the primary outcome, first occurrence of a MACE. According to the statistical analysis plan, a total of 3546 patients would provide 80% power to detect a relative reduction in the annual primary outcome rate from 1.4% for the invasive coronary angiography group to 0.8% for the computed tomography group.[22] In this study, we analysed the effect of gender on primary and secondary endpoints of the DISCHARGE trial as well as interactions between gender and study arm. A post-hoc power analysis using group size and number of events is presented in supplementary table A in web appendix 2.

We compared categorical variables by using χ^2 tests (or Fisher's exact test for small datasets). We compared continuous variables between groups by using the independent samples Student's t test for normally

distributed data or the Mann-Whitney U test for non-normally distributed data.

For the primary endpoint, we calculated cumulative incidences of MACE. Major adverse cardiovascular events included cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction, and non-cardiovascular death and unknown cause of death were considered as competing risks. Follow-up was defined as the period from randomisation until the occurrence of the outcome or otherwise censored at death (non-cardiovascular events and unknown causes of death), loss to follow-up, or the end of the study. We also analysed secondary time to event endpoints such as the composite of MACE and major procedure related complications by using cumulative incidences adjusted for competing risks.[32] We used the sub-distribution Cox proportional hazard model of Fine and Gray to analyse the effect of the study group (computed tomography versus invasive coronary angiography) stratified for gender, as well as the interaction between gender and group. For sensitivity analysis, we used a multivariate sub-distribution Cox proportional hazard model to evaluate adjusted differences in hazard risk of MACE and secondary endpoints by using the covariates gender, randomisation group (invasive coronary angiography/computed tomography), angina type, age, and interaction of gender and group. We report results as hazard ratios and 95% confidence intervals. We evaluated the proportional hazard assumption of the Cox model by using "log-log" plot curves and Schoenfeld residuals.

We used SAS software version 9.4, SPSS for Windows version 26, and the statistical programming language R version 4.0.3 for statistical analyses. In this secondary analysis, we defined statistical significance as a two sided P value of less than 0.05, whereas in the primary analysis a P value of 0.048 was considered significant following a prespecified interim analysis of the primary outcome. We did not adjust for multiple testing. All analyses were done on the intention-to-treat population.

Patient and public involvement

Patient interest groups at all sites were involved in the planning of the study, and all participating patients will be informed about the results of this analysis.

Results

Study population

Between 3 October 2015 and 12 April 2019, 2052 women and 1615 men were recruited at 26 European centres (fig 1). A total of 1031 women were randomised to the computed tomography group (10 withdrew consent and two were randomised in error) and 1021 were randomised to the invasive coronary angiography group (32 withdrew consent and six were randomised in error); the corresponding numbers in men were 802 randomised to the computed tomography group (10 withdrew consent and three were randomised in error) and 813 randomised to the invasive coronary angiography group (37 withdrew consent and six were randomised in error). Overall, 3561 patients (women: 2002 (computed tomography 1019; invasive coronary angiography 983); men: 1559 (computed tomography 789; invasive coronary angiography 770)) were included in the intention-to-treat analysis (fig 1). At 3.5 years, follow-up for the primary endpoint was available in 98.9% (computed tomography 1010; invasive coronary angiography 969) of women and 99.0% (computed tomography 782; invasive coronary angiography 762) of men.

Baseline patient characteristics

Table 1 provides baseline characteristics separately for women and men and stratified by gender and initial test strategy (computed tomography versus invasive coronary angiography); reproductive factors in women are given in supplementary table B in web appendix 2. Women were slightly older (61.8 (SD 9.7) years) than men (58.1 (10.3) years), more often had typical angina as the type of chest pain, and more frequently had arterial hypertension and asthma than did men. Furthermore, smoking was less frequent and the pre-test probability of coronary artery disease was lower in women. Overall, the characteristics of women and men were similar in the two randomised study groups.

Initial test findings and revascularisation

Table 2 shows initial test findings by either computed tomography or invasive coronary angiography, frequency of computed tomography and coronary artery disease tests done during initial management, invasive access site information, and coronary revascularisation. The median time from enrolment to the initial test was longer in the invasive coronary angiography group than in the computed tomography group both for women (10 (interquartile range 1-35) days *v* 3 (0-15) days) and for men (13 (1-41) days *v* 4 (0-13) days).

The frequency of detection of obstructive coronary artery disease was similar with either a computed tomography strategy or an invasive coronary angiography strategy, both in women (201 (19.7%, 95% confidence interval 17.4% to 22.4%) and 179 (18.2%, 16.1% to 21.1%)) and in men (264 (33.5%, 30.4% to 37.2%) and 272 (35.8%, 32.4% to 39.4%)) (table 2). Non-obstructive coronary artery disease was more frequently recorded by computed tomography than by invasive coronary angiography in both genders. With both tests, women more frequently had no signs of coronary artery disease and were less frequently found to have obstructive and/or high risk anatomy coronary artery disease compared with men. In the computed tomography group, the frequency of a non-diagnostic test was similar in women and men (63 (6.2%, 4.8% to 7.9%) *v* 40 (5.1%, 3.7% to 6.9%); table 2).

Invasive procedures were most commonly done using radial access (table 2). Coronary revascularisation was less frequent in women than in men and, for both genders, less frequent in the computed tomography group.

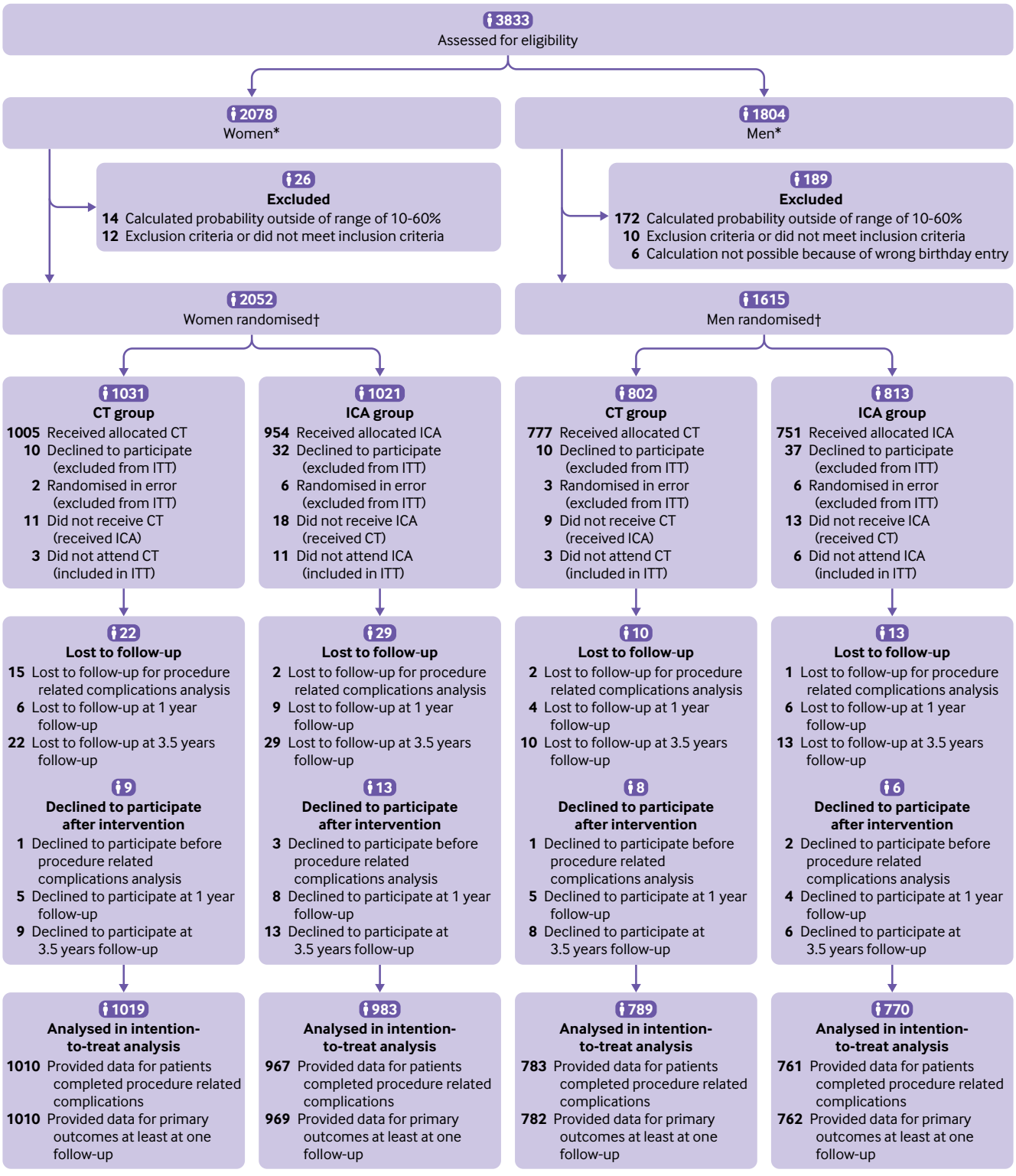


Fig 1 | Flow of patients in study. Overall, 3561 patients (women: 2002 (computed tomography (CT) group 1019; invasive coronary angiography (ICA) group 983); men: 1559 (CT group 789; ICA group 770)) were included in intention-to-treat analysis. Follow-up for primary endpoint was available in 98.9% (CT 1010; ICA 969) of women and 99.0% (CT 782; ICA 762) of men. ITT=intention to treat. *Information on gender not available for one patient. †Randomisation was stratified by gender

Primary and secondary endpoints

The primary endpoint (MACE) occurred with similar frequency in women and men (supplementary table C in web appendix 2). The interaction between gender and study group for MACE was not significant (hazard ratio 1.58, 95% confidence interval 0.68 to 3.66; P=0.29). Subgroup analysis stratified by gender showed a similar risk of having a MACE in the computed tomography and invasive coronary angiography groups in women (22 (2.2%) *v* 24 (2.4%))

Table 1 | Baseline characteristics of women versus men and stratified by gender and initial test strategy (CT *v* ICA). Values are numbers (percentages) unless stated otherwise

Characteristics	Women (n=2002)	Men (n=1559)	Women (n=2002)		Men (n=1559)	
			CT group (n=1019)	ICA group (n=983)	CT group (n=789)	ICA group (n=770)
Mean (SD) age, years	61.8 (9.7)	58.1 (10.3)	61.7 (9.7)	61.9 (9.7)	58.3 (10.6)	57.8 (9.9)
Patients at time of trial enrolment:						
Outpatients	1536 (78.8)	1177 (78.6)	780 (78.9)	756 (78.7)	606 (79.4)	571 (77.8)
Inpatients	414 (21.2)	320 (21.4)	209 (21.1)	205 (21.3)	157 (20.6)	163 (22.2)
Data missing	52 (2.6)	62 (4.0)	30 (2.9)	22 (2.2)	26 (3.3)	36 (4.7)
Type of chest pain:						
Typical angina	460 (23.0)	47 (3.0)	212 (20.8)*	248 (25.2)*	20 (2.5)	27 (3.5)
Atypical angina	909 (45.4)	739 (47.4)	462 (45.3)	447 (45.5)	381 (48.3)	358 (46.5)
Nonanginal chest pain	592 (29.6)	719 (46.1)	322 (31.6)*	270 (27.5)*	355 (45.0)	364 (47.3)
Other chest pain	41 (2.0)	54 (3.5)	23 (2.3)	18 (1.8)	33 (4.2)	21 (2.7)
Mean (SD) pre-test probability of obstructive CAD†	32.6 (10.1)	44.1 (7.8)	32.0 (9.9)*	33.2 (10.3)*	44.2 (7.9)	44.1 (7.7)
ICA referral categories‡:						
Clinical constellation suggesting high event risk, particularly if symptoms were inadequately responding to medical treatment	926 (46.3)	735 (47.1)	496 (48.7)	430 (43.7)	374 (47.4)	361 (46.9)
Severe angina, particularly if symptoms were inadequately responding to medical treatment	482 (24.1)	269 (17.3)	224 (22.0)	258 (26.2)	130 (16.5)	139 (18.1)
Intermediate pre-test probability or LVEF<50% without typical angina following functional testing showing ischaemia	298 (14.9)	254 (16.3)	149 (14.6)	149 (15.2)	128 (16.2)	126 (16.4)
Low or intermediate event risk if symptoms were inadequately responding to medical treatment	179 (8.9)	187 (12.0)	91 (8.9)	88 (9.0)	98 (12.4)	89 (11.6)
Intermediate pre-test probability or LVEF<50% without typical angina following non-diagnostic functional testing	57 (2.8)	46 (3.0)	29 (2.8)	28 (2.8)	23 (2.9)	23 (3.0)
Other§	52 (2.6)	62 (4.0)	27 (2.6)	25 (2.5)	33 (4.2)	29 (3.8)
Data missing	8 (0.4)	6 (0.4)	3 (0.3)	5 (0.5)	3 (0.4)	3 (0.4)
Cardiovascular risk factors:						
Arterial hypertension	1255 (63.0)	867 (55.8)	653 (64.5)	602 (61.5)	449 (57.1)	418 (54.6)
Diabetes mellitus	309 (15.5)	248 (16.0)	143 (14.1)	166 (17.0)	120 (15.2)	128 (16.8)
Hyperlipidaemia	998 (49.9)	708 (45.4)	521 (51.1)	477 (48.5)	353 (44.7)	355 (46.1)
Valve disease	121 (6.1)	68 (4.4)	57 (5.6)	64 (6.5)	37(4.7)	31 (4.0)
Stroke	51 (2.6)	40 (2.6)	30 (3.0)	21 (2.1)	17 (2.2)	23 (3.0)
Transient ischaemic attack	43 (2.2)	24 (1.5)	21 (2.1)	22 (2.2)	11 (1.4)	13(1.7)
Prolonged ischaemic neurological deficit	4 (0.2)	1 (0.1)	2 (0.2)	2 (0.2)	0	1 (0.1)
Carotid artery disease	46 (2.3)	36 (2.3)	23 (2.3)	23 (2.3)	15 (1.9)	21 (2.7)
Family history of premature CAD	658 (33.0)	405 (26.1)	321 (31.7)	337 (34.4)	194 (24.7)	211 (27.5)
Data missing	11 (0.5)	6 (0.4)	7 (0.7)	4 (0.4)	2 (0.3)	4 (0.5)
Pulmonary risk factors:						
Asthma	148 (7.4)	66 (4.3)	89 (8.8)	59 (6.0)	34 (4.3)	32 (4.2)
Chronic obstructive pulmonary disease	85 (4.3)	68 (4.4)	41 (4.1)	44 (4.5)	31 (3.9)	37 (4.8)
Data missing	11 (0.5)	6 (0.4)	7 (0.7)	4 (0.4)	2 (0.3)	4 (0.5)
Smoking status:						
Current smokers	319 (16.5)	324 (21.4)	168 (17.1)	151 (15.9)	175 (22.9)	149 (20.0)
Former smokers	512 (26.5)	612 (40.5)	243 (24.7)	269 (28.3)	297 (38.8)	315 (42.2)
Never smoked	1103 (57.0)	575 (38.1)	571 (58.1)	532 (55.9)	293 (38.3)	282 (37.8)
Data missing	68 (3.4)	48 (3.1)	37 (3.6)	31 (3.2)	24 (3.0)	24 (3.1)
Cardiovascular drugs:						
Statin	918 (46.2)	677 (43.7)	473 (46.8)	445 (45.5)	335 (42.7)	342 (44.7)
Antiplatelet agent	986 (49.6)	755 (48.7)	488 (48.3)	498 (51.0)	369 (47.1)	386 (50.5)
β blocker	909 (45.7)	584 (37.7)	453 (44.8)	456 (46.7)	300 (38.3)	284 (37.1)
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	956 (48.1)	711 (45.9)	502 (49.7)	454 (46.5)	366 (46.7)	345 (45.1)
Calcium antagonist	435 (21.9)	282 (18.2)	227 (22.5)	208 (21.3)	141 (18.0)	141 (18.4)
Nitrates	231 (11.6)	162 (10.5)	120 (11.9)	111 (11.4)	83 (10.6)	79 (10.3)
Data missing	14 (0.7)	10 (0.6)	8 (0.8)	6 (0.6)	5 (0.6)	5 (0.6)
Mean (SD) body mass index	28.7 (5.4) (n=1940)	29.1 (4.8) (n=1517)	28.8 (5.4) (n=981)	28.5 (5.4) (n=959)	29.0 (4.9) (n=763)	29.1 (4.7) (n=754)
At least one functional test performed before initial test:	679 (33.9)	526 (33.7)	343 (33.7)	336 (34.2)	256 (32.4)	270 (35.1)
Positive	298 (14.9)	254 (16.3)	149 (14.6)	149 (15.2)	128 (16.2)	126 (16.4)
Negative	324 (16.2)	226 (14.5)	165 (16.2)	159 (16.2)	105 (13.3)	121 (15.7)
Non-diagnostic	57 (2.8)	46 (3.0)	29 (2.8)	28 (2.8)	23 (2.9)	23 (3.0)

CAD=coronary artery disease; CT=computed tomography; ICA=invasive coronary angiography; LVEF=left ventricular ejection fraction; SD=standard deviation.
*Statistically significant differences were found between CT and ICA strategies in women for typical angina (P=0.019), nonanginal chest pain (P=0.043), and pre-test probability of obstructive CAD (P=0.046).
†Calculated pre-test probability of CAD using automated calculation,[17] integrated into web based system of electronic case report forms, which applied updated model of Diamond and Forrester method using patients' age, gender, and type of stable chest pain.
‡ICA referral categories were defined according to European guidelines for management of stable CAD.[27]
§Other ICA referral categories included cannot undergo stress imaging (women 10 (0.5%) *v* men 8 (0.4%)), LVEF<50% and typical angina (women 20 (1.0%) *v* men 16 (0.9%)), mild symptoms with medical treatment in patients in whom non-invasive risk stratification indicates high event risk and revascularisation is considered for improvement of prognosis (women 14 (0.7%) *v* men 31 (1.8%)), and inconclusive diagnosis on non-invasive testing or conflicting results from different noninvasive methods (women 8 (0.4%) *v* men 5 (0.3%)) and special professions, such as pilots, owing to regulatory issues (women: 0 *v* men: 2 (0.1%)).

Table 2 | Comparison of diagnostic strategies during initial care. Values are numbers (percentages, 95% confidence intervals) unless stated otherwise

	Women		Men	
Measures	**CT group (n=1019)**	**ICA group (n=983)**	**CT group (n=789)**	**ICA group (n=770)**
CTs as initial test performed	1005 (98.6, 97.8 to 99.2)	18 (1.8, 1.1 to 2.9)	777 (98.5, 97.4 to 99.2)	13 (1.7, 0.9 to 2.9)
ICAs as initial test performed	11 (1.1, 0.5 to 1.9)	954 (97.0, 95.8 to 98.0)	9 (1.1, 0.6 to 2.1)	751 (97.5, 96.3 to 98.5)
Patients who did not attend scheduled intervention	3 (0.3, 0.1 to 0.9)	11 (1.1, 0.6 to 2.0)	3 (0.4, 0.1 to 1.0)	6 (0.8, 0.3 to 1.7)
Median (IQR) time to initial test, days*	3 (0-15) (95% CI 3.0 to 6.0)	10.0 (1-35) (95% CI 7.0 to 14.0)	4 (0-13) (95% CI 2.0 to 6.0)	13 (1-41) (95% CI 8.0 to 19.0)
Coronary findings by initial test:				
Obstructive CAD (≥50%)	201 (19.7, 17.4 to 22.4)	179 (18.2, 16.1 to 21.1)	264 (33.5, 30.4 to 37.2)	272 (35.8, 32.4 to 39.4)
1 vessel CAD	75 (7.4, 5.9 to 9.1)	75 (7.6, 6.1 to 9.5)	80 (10.1, 8.1 to 12.5)	106 (13.8, 11.4 to16.4)
2 vessel CAD	24 (2.4, 1.6 to 3.4)	26 (2.6, 1.7 to 3.9)	35 (4.4, 3.1 to 6.1)	48 (6.2, 4.7 to 8.1)
High risk anatomy CAD†	102 (10.0, 8.3 to 12.0)	78 (7.9, 6.3 to 9.8)	149 (18.9, 16.2 to 21.8)	118 (15.3, 12.9 to 18.0)
Non-obstructive CAD (1-49%)	367 (36.0, 33.3 to 39.3)	218 (22.5, 19.9 to 25.3)	288 (36.8, 30.4 to 37.2)	175 (23.1, 20.1 to 26.2)
No signs of CAD	382 (37.7, 34.7 to 40.8)	567 (58.6, 55.5 to 61.8)	191 (24.4, 21.4 to 27.6)	310 (40.8, 37.3 to 44.4)
Non-diagnostic‡	63 (6.2, 4.8 to 7.9)	3 (0.3, 0.0 to 0.9)	40 (5.1, 3.7 to 6.9)	2 (0.3, 0.0 to 1.0)
Data missing§	6 (0.6)	16 (1.6)	6 (0.8)	11 (1.4)
CTs during initial management¶	1006 (98.5, 97.6 to 99.2)	20 (2.0, 1.2 to 3.1)	778 (98.5, 97.4 to 99.2)	15 (1.9, 1.1 to 3.1)
ICAs during initial management:	167 (16.4, 14.2 to 18.8)	955 (97.0, 95.8 to 98.0)	237 (30.0, 26.9 to 33.3)	753 (97.7, 96.3 to 98.6)
Radial artery access	147 (88.8, 83.1 to 92.9)	845 (88.6, 83.6 to 88.1)	196 (82.7, 21.9 to 28.0)	669 (88.8, 84.3 to 89.2)
Femoral artery access	19 (11.4, 6.6 to 16.2)	92 (9.6, 7.6 to 11.4)	37 (15.6, 3.3 to 6.4)	73 (9.7, 7.5 to 11.8)
Other arterial access or data missing**	1 (0.6)	18 (1.8)	4 (1.7)	11 (1.5)
Coronary revascularisations during initial management	90 (8.8, 7.2 to 10.7)	114 (11.6, 9.7 to 13.7)	141 (17.9, 15.3 to 20.7)	193 (25.1, 22.1 to 28.2)

CAD=coronary artery disease; CI=confidence interval; CT=computed tomography; ICA=invasive coronary angiography; IQR=interquartile range.
*Time to initial test results are cumulative incidence estimates.
†High risk anatomy CAD was defined by initial test as any three vessel CAD, left main coronary artery stenosis, proximal left anterior descending coronary artery stenosis, or any combination of these.
‡Non-diagnostic test was defined as relevant artefact in CT or poor opacification in CT or ICA that could conceal ≥50% stenosis in vessel with reference diameter of ≥2 mm without obstructive coronary artery stenosis elsewhere in same patient. Patients were recommended to undergo further testing in case of non-diagnostic initial test results.
§23 did not attend initial test (women: CT 3 *v* ICA 11; men: CT 3 *v* ICA 6), 12 incomplete test (women: CT 1 *v* ICA 5; men: CT 3 *v* ICA 3), 3 data not documented or lost (women: CT 2 *v* ICA 0; men: CT 0 *v* ICA 1), and 1 test findings missing (women: CT 0 *v* ICA 0; men: CT 0 *v* ICA 1).
¶These numbers include CT tests following ICA tests and ICA tests following CT tests in both randomisation groups.
**Other access for ICA included 25 radial and femoral artery access (women: CT 1 *v* ICA 13; men: CT 3 *v* ICA 8), 6 brachial artery access (women: CT 0 *v* ICA 3; men: CT 1 *v* ICA 2), 1 radial and brachial artery access (women: CT 0 *v* ICA 1; men: CT 0 *v* ICA 0), and 2 data on arterial access not documented or data lost (women: CT 0 *v* ICA 1; men: CT 0 *v* ICA 1).

and men (16 (2.0%) *v* 28 (3.6%)) (fig 2). The results for the individual components of the primary endpoint MACE are shown in table 3 and supplementary figures A-C in web appendix 2.

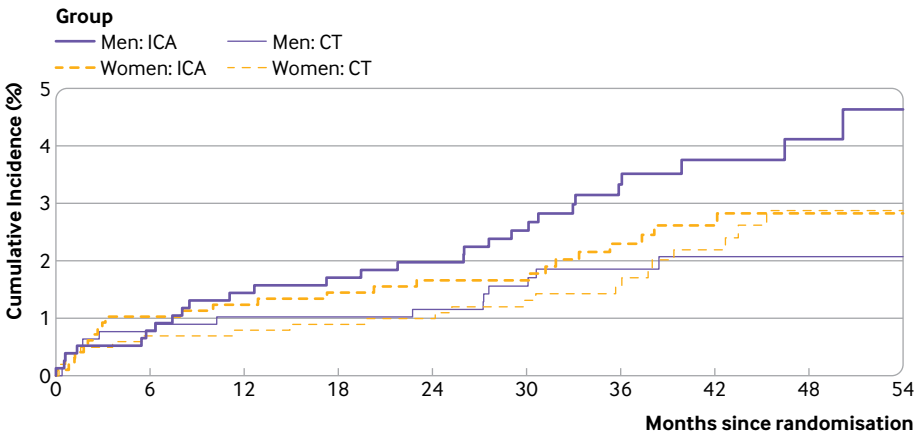
The expanded MACE composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack, or major procedure related complication occurred with similar frequency in women and men (supplementary table C in web appendix 2). The interaction between gender and study group for the expanded MACE composite was not significant (hazard ratio 1.31, 0.65 to 2.67; P=0.45). We did further subgroup analysis stratified by gender. In men, the expanded MACE composite endpoint occurred less frequently in the computed tomography group than in the invasive coronary angiography group (22 (2.8%) *v* 41 (5.3%); hazard ratio 0.52, 0.31 to 0.87) (table 3 and fig 3). In women, the secondary expanded MACE composite was similar in the computed tomography and invasive coronary angiography groups (table 3 and fig 3). Rates of secondary additional composite endpoints were similar for the two test strategies in both women and men (table 3 and supplementary figures D-F in web appendix 2).

Major procedure related complications occurred with similar frequency in women and men (supplementary table C in web appendix 2). We found no significant interaction between gender and study group for major procedure related complications (hazard ratio 0.28, 0.06 to 1.33; P=0.11). In women, the risk of having a major procedure related complication was lower in the computed tomography group than in the invasive coronary angiography group (3 (0.3%) *v* 21 (2.1%); hazard ratio 0.14, 0.04 to 0.46) whereas no such difference was noted in men (table 3 and fig 4). Most major procedure related complications were observed in relation to invasive coronary angiography procedures, and the frequency was highest in women allocated to the invasive coronary angiography group (supplementary tables D-H in web appendix 2). Major procedure related complications related to invasive coronary angiography with percutaneous intervention were lower in women when invasive coronary angiography followed initial computed tomography (supplementary table G in web appendix 2).

In the sensitivity analysis including, for instance, age and chest pain as covariates, we found a smaller risk for expanded MACE in women. The interactions between gender and study group for MACE, expanded MACE, and major procedure related complications were also not significant (supplementary tables I and J in web appendix 2).

Discussion

In this predefined gender subgroup analysis of the computed tomography and invasive coronary angiography groups in the DISCHARGE trial, in which randomisation was stratified by gender and centre, we found no evidence for a difference between women and men in the benefit of using computed tomography rather than invasive coronary angiography as the initial



No at risk

Men: ICA								
770	756	750	737	731	660	524	355	230
Women: ICA								
983	958	942	927	923	836	666	468	296
Men: CT								
789	774	769	763	760	672	540	376	235
Women: CT								
1019	999	989	978	971	869	704	489	307

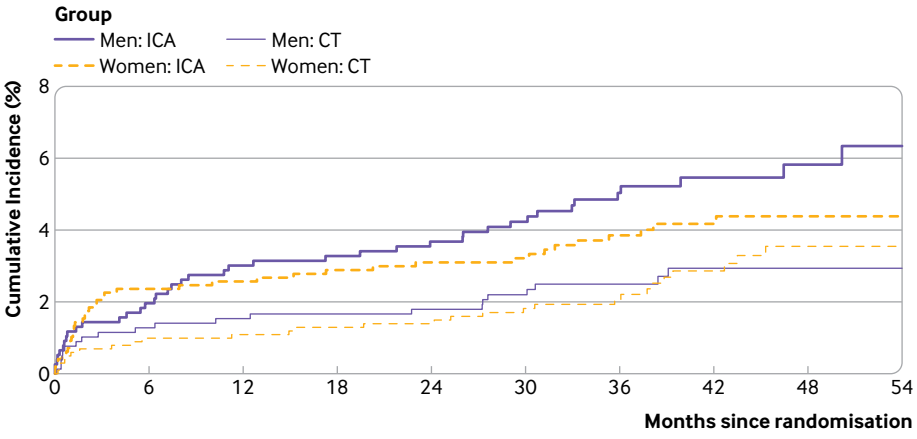
Fig 2 | Cumulative incidence curves for primary endpoint (major adverse cardiovascular events (MACE)). At median follow-up of 3.5 years, no differences existed between computed tomography (CT) and invasive coronary angiography (ICA) for either women or men (hazard ratios for these comparisons are provided in figure S3 of main clinical publication of total patient population included in DISCHARGE)[22]

diagnostic test for the management of stable chest pain in patients with an intermediate pre-test probability of coronary artery disease. Initial computed tomography was associated with fewer major procedure related complications in women and a lower frequency of the expanded MACE composite endpoint in men. A

Table 3 | Primary and secondary endpoints stratified by gender and allocation group. Values are numbers (percentages) unless stated otherwise

	Women			Men			
Endpoints	CT group (n=1019)	ICA group (n=983)	Hazard ratio (95% CI)	CT group (n=789)	ICA group (n=770)	Hazard ratio (95% CI)	Interaction P value group v gender value
Components of MACE:	22 (2.2)	24 (2.4)	0.88 (0.49 to 1.56)	16 (2.0)	28 (3.6)	0.56 (0.30 to 1.03)	0.29
Non-fatal myocardial infarction	14 (1.4)	12 (1.2)	1.12 (0.52 to 2.41)	9 (1.1)	8 (1.0)	1.11 (0.43 to 2.89)	
Non-fatal stroke	6 (0.6)	9 (0.9)	0.64 (0.23 to 1.79)	4 (0.5)	11 (1.4)	0.35 (0.11 to 1.11)	
Cardiovascular death	2 (0.2)	4 (0.4)	0.48 (0.09 to 2.64)	5 (0.6)	10 (1.3)	0.49 (0.17 to 1.42)	
Secondary endpoints							
Expanded MACE composite: cardiovascular death, myocardial infarction, stroke, transient ischaemic attack, or major procedure related complication	28 (2.7)	39 (4.0)	0.68 (0.42 to 1.11)	22 (2.8)	41 (5.3)	0.52 (0.31 to 0.87)	0.45
Additional composite endpoints:							
Vascular death or myocardial infarction	14 (1.4)	14 (1.4)	0.96 (0.46 to 2.00)	11 (1.4)	10 (1.3)	1.09 (0.46 to 2.56)	
Cardiac death or myocardial infarction	16 (1.6)	14 (1.4)	1.09 (0.53 to 2.24)	11 (1.4)	16 (2.1)	0.68 (0.32 to 1.46)	
All cause death, myocardial infarction, or stroke	34 (3.3)	36 (3.7)	0.9 (0.57 to 1.44)	34 (4.3)	47 (6.1)	0.7 (0.45 to 1.09)	
Major procedure related complications during initial management:*	3 (0.3)	21 (2.1)	0.14 (0.04 to 0.46)	6 (0.8)	12 (1.6)	0.49 (0.18 to 1.29)	0.11
Non-fatal myocardial infarction	1 (0.1)	8 (0.8)		2 (0.3)	2 (0.3)		
Non-fatal stroke	0	0		0	1 (0.1)		
Cardiac arrhythmia (ventricular tachycardia, ventricular fibrillation)	0	6 (0.6)		0	0		
Further complications prolonging hospital admission by ≥24 h	0	6 (0.6)		4 (0.5)	5 (0.6)		
Dissection (coronary, aortic)	2 (0.2)	1 (0.1)		0	1 (0.1)		
Cardiac arrest	0	0		0	2 (0.3)		
Cardiac tamponade	0	0		0	1 (0.1)		

CT=computed tomography; CI=confidence interval; ICA=invasive coronary angiography; MACE=major adverse cardiovascular events.
Percentage results for all major procedure related complication are cumulative incidence estimates, and percentage results for individual complications are proportions.
*Complete list of all major procedure related complications and more detailed information on further complications prolonging hospitalisation by ≥24 h are provided in supplementary table C in web appendix 2. Detailed list of all major procedure related complications in both randomisation groups and their relation to procedures are provided in supplementary tables D-G in web appendix 2.



No at risk

Men: ICA								
770	747	738	725	718	648	515	348	227
Women: ICA								
983	945	929	913	909	821	655	458	289
Men: CT								
789	770	766	759	756	668	537	373	232
Women: CT								
1019	996	986	974	967	865	701	485	304

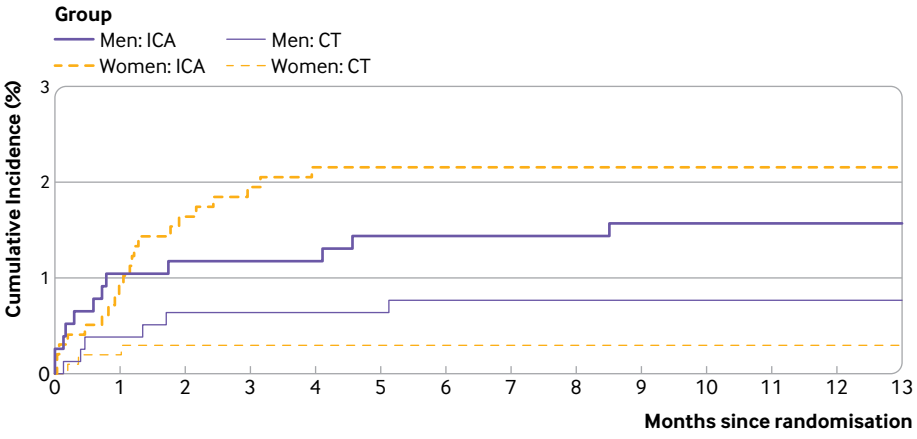
Fig 3 | Cumulative incidence curves for secondary endpoint (expanded major adverse cardiovascular events (MACE) composite: cardiovascular death, myocardial infarction, stroke, transient ischaemic attack, or major procedure related complication). Expanded MACE composite endpoint occurred less frequently in men in computed tomography (CT) group compared with invasive coronary angiography (ICA) group (hazard ratio 0.52, 95% confidence interval 0.31 to 0.87). In women, expanded MACE composite was similar in CT group and ICA group (hazard ratio 0.68, 0.42 to 1.11)

sensitivity analysis showed a smaller risk for expanded MACE in women but again no significant interactions between gender and study group for the primary and secondary endpoints.

Comparison with other studies

Our results corroborate and further extend the findings of previous post-hoc gender specific investigations conducted in the PROMISE, ISCHEMIA, and SCOT-HEART diagnostic strategy trials.[2-4] In accordance with these investigations, we found that women with chest pain had less obstructive epicardial coronary artery disease and more frequently had normal coronary arteries compared with men. Importantly, the proportion of patients in whom obstructive coronary artery disease was found was similar with either a computed tomography strategy or an invasive coronary angiography strategy, in both women (19.7% and 18.2%) and men (33.5% and 35.3%), suggesting comparable diagnostic accuracy of the two investigations to identify obstructive disease. Interestingly, non-obstructive coronary artery disease was more frequently detected by computed tomography than by invasive coronary angiography, and the frequency of detected non-obstructive disease was similar in women and men. This higher sensitivity of computed tomography to detect non-obstructive coronary artery disease compared with invasive coronary angiography may have important clinical implications in terms of treatment because non-obstructive disease is associated with poorer long term outcome.[33] As recently highlighted by Al-Lamee and colleagues in *The BMJ*, aggressive risk factor modification with medical therapy in patients with stable coronary artery disease has the greatest effect on the long term risk of myocardial infarction and death.[34] That, in both genders, preventive medical therapy could be improved when guided by computed tomography seems plausible. The frequency of non-diagnostic computed tomography was similar in women and men, ranging from 5% to 6%, in accordance with similar large scale studies using computed tomography scanners with 64 slices and higher.[35 36] On the other hand, a frequency of non-diagnostic computed tomography of 3.7% was previously reported when exclusively 320 slice computed tomography technology was used, suggesting that the frequency of non-diagnostic computed tomography might be lower if more advanced computed tomography technology was used consistently.[36]

With one exception, all major procedure related complications were attributable to invasive coronary angiography without or with subsequent coronary revascularisation. One man undergoing computed tomography experienced an episode of bradycardia, which prolonged hospital admission by at least 24 hours and was probably attributable to pre-treatment with a β blocker (see supplementary table E in appendix 2). The overall risk of having a major procedural complication was not significantly different when we compared all women and all men in the DISCHARGE cohort. This finding is consistent with reports suggesting an overall



No at risk

Men: ICA												
770	757	755	753	752	750	750	750	749	748	748	747	746
Women: ICA												
983	965	956	951	948	947	947	946	945	944	944	944	932
Men: CT												
789	779	777	776	775	775	774	773	773	773	773	773	771
Women: CT												
1019	1010	1007	1006	1005	1003	1003	1003	1003	1002	1002	1002	994

Fig 4 | Cumulative incidence curves for major procedure related complications. In women, major procedure related complications occurred less frequently in computed tomography (CT) group than in invasive coronary angiography (ICA) group (hazard ratio 0.14, 0.04 to 0.46), whereas no difference was noted in men (0.49, 0.18 to 1.29)

decline in invasive coronary procedural complications over the past decade, especially in women. This trend reduces the previously reported gender difference,[13 15] and it likely reflects the more common general use of radial access.[37] Nevertheless, women randomised to an initial computed tomography strategy had a significantly lower risk of a major procedure related complication than did women randomised to an initial invasive coronary angiography strategy. Most likely, this observation reflects the lower prevalence of coronary artery disease needing invasive investigation and coronary revascularisation, especially in women, highlighting the positive contribution of computed tomography as a gatekeeper for invasive investigation and treatment in this setting, as well as a lower risk of invasive coronary angiography and percutaneous coronary intervention in patients with an earlier computed tomography scan.

In both women and men, a strategy of initial computed tomography resulted in a rate of MACE that was not significantly different from that with a strategy of initial invasive coronary angiography during a median follow-up period of 3.5 years. However, we noted a borderline trend to improved outcome in men, which reached statistical significance for the predefined secondary expanded MACE composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack, or major procedural complications. The clinical benefit for most patients with stable chest pain undergoing guideline defined examination and treatment is relief of chest pain, and some patients also have improved clinical outcomes.[38 39] The strategy of initial computed tomography in the DISCHARGE trial comprised a stringent clinical triage based on computed tomography angiography findings, including referral for an invasive procedure for coronary revascularisation, optimal medical therapy, or search for non-cardiac causes.[22] As previously reported, after a median follow-up of 3.5 years, most women and men in the DISCHARGE cohort had achieved symptom relief, and the rates were similar for an initial computed tomography strategy and an initial invasive coronary angiography strategy.[22] Evidently, the important goal of relief of chest pain is safely achieved with either strategy and in women and men alike.

Both women and men were included in our trial if they had a low to intermediate pre-test probability of 10-60% of disease, taking into account factors such as age, gender, and type of chest pain symptoms.[17] We defined his approach according to clinical guidelines in order to optimise the diagnostic pathway in patients with chest pain and coronary artery disease.[27] In this context, we note that women included in our trial more frequently had typical angina pectoris and were slightly older than men, which probably reflects selection as a consequence of the features of the pre-test probability tool used. Nevertheless, the prevalence of coronary artery disease predicted by the tool in women and men was only moderately above the rates we found with either computed tomography or invasive coronary angiography (approximately 10% in men and 13% in women).

Strengths and weaknesses of study

Strengths of our study include the multicentre pragmatic design, in which women and men were randomised in a stratified fashion to either an initial computed tomography strategy or an initial invasive coronary angiography strategy. Furthermore, women and men were almost equally represented, with a high adherence to follow-up in both genders, facilitating a statistically plausible comarison.[40] A limitation of the study is, as previously noted, a lower than expected event rate during the course of the trial.[22] This might reflect a general temporal trend towards fewer procedural complications related to invasive diagnosis and treatment, optimised medical treatment, and a generally improved adherence to lifestyle recommendations in participating countries.[41] The natural history of coronary atherosclerosis may differ between males and females. Patients in our study were categorised according to self-reported gender (women and men) not sex, and the extent of heterogeneity within each gender group with regard to sex is therefore not known. The results should therefore be interpreted with caution.

Conclusions

We found no evidence for a difference between women and men in the benefit of using computed tomography rather than invasive coronary angiography as the initial diagnostic test for the management of stable chest pain in patients with an intermediate pre-test probability of coronary artery disease. Computed tomography as the initial diagnostic test in this patient population resulted in a lower frequency of procedural complications in women and a lower frequency of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack, or major procedure related complications in men compared with a strategy of initial invasive coronary angiography. Both men and women benefitted from computed tomography as the initial diagnostic test.

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Contributors: The DISCHARGE Trial Group investigators contributed to data collection, approved the manuscript after reviewing the findings and interpretation, provided critical revisions of the manuscript for important intellectual content, gave final approval of the version to be published, and are accountable for the work. RH and MD developed the concept and design of the study. KFK, MBosserdt, PM, and MD acquired, analysed, and interpreted the data. KFK, MBosserdt, and MD drafted the manuscript. PM and LMS-H did the statistical analysis. AEN, MBosserdt, ME, and MD supervised the trial. KFK and MBosserdt contributed equally. MD is the guarantor. The corresponding author affirms that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: This study was approved by the ethics committee of the Charité –Universitätsmedizin Berlin (EA1/294/13) and by the German Federal Office for Radiation Protection (Z5–2246/2–2014-001). On the basis of this, all other clinical partners received ethical approval as required by national law. All patients provided written informed consent.

Data sharing: Individual participant data that underlie the results reported in the published article after de-identification will be shared with researchers who provide a sound proposal approved by the Dissemination Committee of the DISCHARGE trial. Proposals should be directed to discharge.eu@charite.de.

The lead author (KFK) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We plan to share this work through multiple social media channels—for example, on Twitter: @team_dewey, @PalMaurovich, @kkofoed1, @RigsHeart, @JRodriPalomares, @lucasabalTA, @ColinBerryMD, @JuhaniKnuuti, @gudrunfeuchtner, @zsofidrobni, @Balint_CCTA, @AdrianeNapp, @UCDProfDodd, and @ProfDewey. On publication of the manuscript, appropriate communications will be made with the press and the trial website (https://www.dischargetrial.eu/) will be used to share results with appropriate citations to the work.

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Supplementary information: Appendix 1: CONSORT checklist
Supplementary information: Appendix 2: Additional analyses
Supplementary information: Full list of author affiliations