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Outcomes in patients with a first episode of chest pain undergoing early coronary CT imaging

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ABSTRACT

Objectives To investigate the impact of a CT-first strategy on all-cause and cardiovascular mortality in patients presenting with chest pain in outpatient cardiology clinics.

Methods Patients with a first presentation of suspected angina pectoris were identified and their data linked to the registrations of Statistics Netherlands for information on mortality. The linked database consisted of 33 068 patients. CT-first patients were defined as patients with a CT calcium score and coronary CT angiography, within 6 weeks after their initial visit. Propensity score matching (1:5) was used to match patients with and without a CT-first strategy. After matching, 12 545 patients were included of which 2308 CT-first patients and 10 237 patients that underwent usual care.

Results Mean age was 57 years, 56.3% were women and median follow-up was 4.9 years. All-cause mortality was significantly lower in CT-first patients (n=43, 1.9%) compared with patients without CT (n=363, 3.5%) (HR: 0.51, 95% CI 0.37 to 0.70). Furthermore, CT-first patients were more likely to receive cardiovascular preventative and antianginal medication (aspirin: 44.9% vs 27.1%, statins: 48.7% vs 30.3%, beta-blockers: 37.8% vs 25.5%, in CT-first and without CT-first patients, respectively) and to undergo downstream diagnostics and interventions (coronary interventions: 8.5% vs 5.7%, coronary angiography: 16.2% vs 10.6% in CT-first and without CT-first patients, respectively).

Conclusions In a real-world regular care database, a CT-first strategy in patients suspected of angina pectoris was associated with a lowering of all-cause mortality.

INTRODUCTION

Longitudinal studies of employing cardiac CT imaging including both coronary calcium scoring (CACS) and cardiac CT angiography (CCTA) in patients presenting with chest pain have demonstrated incremental prognostic value compared with traditional risk profiling algorithms.¹ Higher CACS is associated with mortality^{2,3} and has added value to the Framingham Risk Score for predicting cardiovascular events.⁴ The introduction of CCTA showed even greater promise as a tool to define risk of myocardial infarction⁵ and coronary revascularisation⁶ compared with CACS. Prospectively randomised trials showed that CCTA was superior to functional cardiac testing for cardiovascular endpoints.^{7,8}

Until the results of the SCOT-HEART (Scottish COmputed Tomography of the HEART Trial) study were published,⁵ CCTA was only adopted by the guidelines of the National Institute for Health and Care Excellence in the UK.⁹ The SCOT-HEART study randomised patients presenting with chest pain in the cardiology outpatient clinic to either CCTA initiated, the so-called CT-first strategy, or routine clinical care. Patients randomised to the CCTA arm showed only about half of the fatal and non-fatal myocardial infarctions after a 5-year follow-up,⁵ although these results were not in line with the previously published PROMISE-trial⁸ and multiple registry studies.^{10,11} Nevertheless, these results prompted the European Society of Cardiology to accord CCTA a class I recommendation for the diagnosis of coronary artery disease (CAD) in symptomatic patients in the renewed European Society of Cardiology (ESC) guidelines of 2019.¹²

However, the results of SCOT-HEART might not be generalisable to a routine care population who are expected to have a higher likelihood of mortality, since randomised trials may induce an overestimation of benefit due to the so-called healthy volunteer inclusion bias in trials.^{13,14} Furthermore, multiple patient groups are often under-represented in clinical studies, such as women,¹⁵ the elderly, non-white ethnicities and patients with comorbidities.^{16,17} Therefore, the impact of a CT-first strategy for patients with chest pain in regular care is still unknown.^{10,11}

The use of data from real-world databases to assess the utility of cardiac CT may aid in defining associations between patient variables and outcomes in the general population. Moreover, real-world data may help to vindicate results of clinical trials, especially with the inclusion of substantial numbers of all relevant patient groups. Thus, we used a regular care database¹⁸ to investigate all-cause and cardiovascular mortality in patients suspected of angina pectoris, who underwent CT calcium score and CCTA following their first visit, and compared this with a propensity score (PS) matched control group from the same database, who were subjected to regular care without cardiac CT.

METHODS

Study population

The CCN database consists of 109 151 patients who visited one of the CCN's outpatient cardiology clinics between 2007 and 2018. These centres



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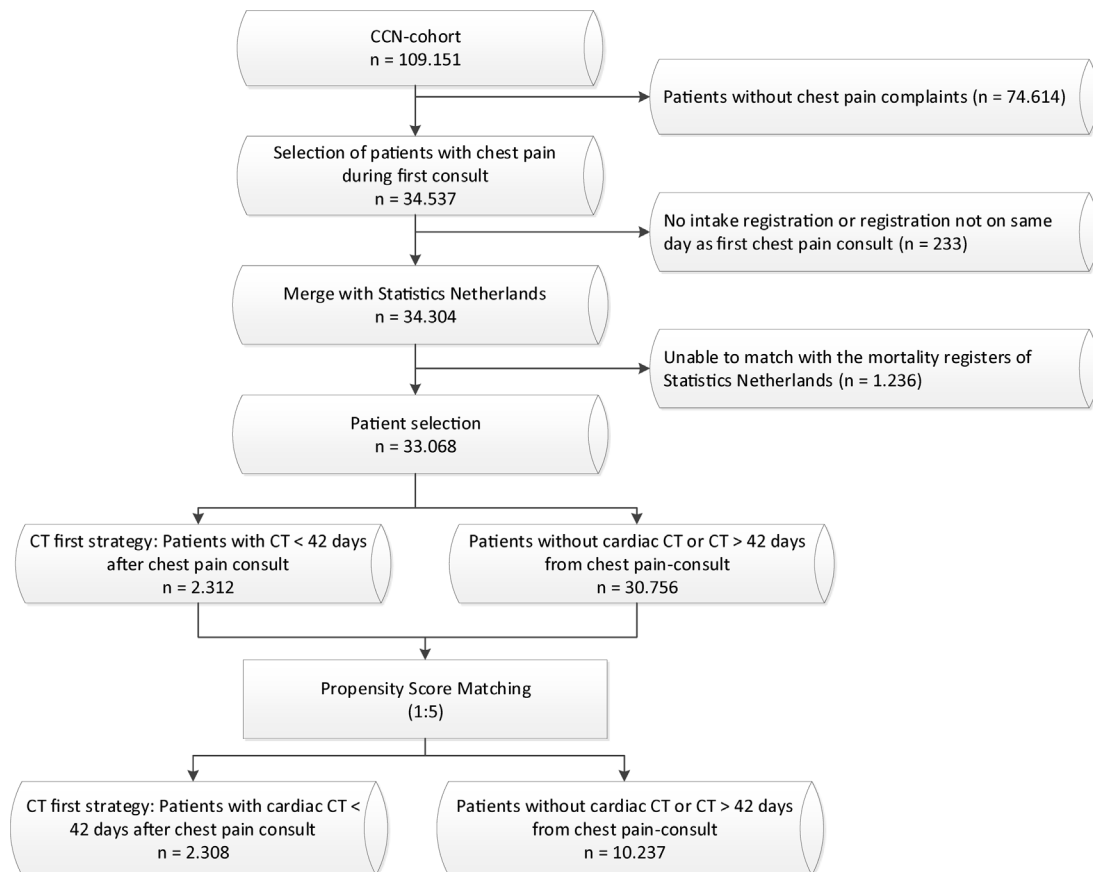


Figure 1 Flow chart of patient selection. CCN, Cardiology Centers of the Netherlands.

are known for their homogenised and structured approach to investigate patients with cardiovascular complaints. A detailed description of the CCN database has been published.¹⁸ Patients with chest pain suspected to be angina pectoris, who presented for the first time at one of the diagnostic centres, were included. The study population was then split in two groups: patients with a cardiac CT within 6 weeks after their first visit, the CT-first strategy, and patients without this diagnostic procedure. Cardiac CT included a scanning protocol for calcium scoring and CCTA. The decision for referral for cardiac CT was made by the treating cardiologist. The type of CT scanner was based on availability in the referenced centres. Follow-up of the population was obtained through linking with the population database of Statistics Netherlands (CBS). **Figure 1** outlines the selection of the study population.

The Cardiology Centers of the Netherlands data were made available under implied consent and transferred to the University Medical Center Utrecht under the Dutch Personal Data Protection Act. This study used data collected during the regular care process and did not subject participants to additional procedures or impose behavioural patterns on them. The Medical Research Ethics Committee of the University Medical Center Utrecht declared that research within the CCN database does not meet the Dutch Medical Research Involving Human Subjects Act (proposal number 17/359).

Study variables

Patient characteristics, prior comorbidities, risk factors, family history and a general medical history were obtained from the electronic health records (EHRs) of the patient. Medication use was extracted from pharmaceutical prescription data. Residential

region of the patient was obtained through four-digit postal code. Chest pain was characterised as typical, atypical or non-anginal, according to Diamond^{12 19} and obtained through retrieval of text variables in the EHR. We also included the results from the stress ECG recording to ensure comparability between patients with and without a CT-first strategy.

Short-term and long-term outcome

All-cause mortality and cardiovascular mortality were the primary and secondary outcome in the analyses, respectively. Other secondary outcomes included registration of diagnostic and therapeutic procedures in the EHR. Diagnostics included stress ECG recording, functional imaging (cardiac MRI, positron emission tomography and single-photon emission computed tomography), invasive coronary angiography (CAG) and cardiac CT more than 6 weeks after the first visit to CCN. Therapeutic procedures were percutaneous coronary intervention and coronary artery bypass grafting. Moreover, prescribed medication changes during and after the chest pain consult were evaluated and compared between the groups. This analysis focused primarily on the value of a cardiac CT in the diagnostic trajectory of the patient. We did not evaluate the association between results of cardiac CT and primary and secondary outcomes.

Missing data

Missing data in variables required for analysis were handled by multiple imputation for chained equations (MICE; 10 iterations, 10 imputed datasets) with the R-package *mice* (V.3.8.0).²⁰ However, for the presence of a family history, missing data were not at random. Therefore, missing values for this variable

Table 1 Baseline table of total population and PS matched sample

	Original sample		Matched sample			Missing	
	Overall	Patients without a CT-first strategy	CT-first	Overall	Patients without a CT-first strategy		CT-first
n	33 068	30 756	2312	12 545	10 237	2308	
Age (mean (SD))*†	56 (13.41)	55 (13.63)	57 (9.85)	57 (12.62)	57 (13.16)	57 (9.85)	0.0
Female (%)**†	17 622 (53.3)	16 329 (53.1)	1293 (55.9)	7068 (56.3)	5779 (56.5)	1289 (55.8)	0.0
Hypertension (%)**†	9668 (29.4)	8966 (29.3)	702 (30.4)	3920 (31.2)	3220 (31.5)	700 (30.3)	0.5
Dyslipidaemia (%)**†	5475 (16.6)	5084 (16.6)	391 (16.9)	2127 (17.0)	1737 (17.0)	390 (16.9)	0.5
Diabetes (%)**†	2734 (8.3)	2559 (8.4)	175 (7.6)	978 (7.8)	803 (7.8)	175 (7.6)	0.6
Height (mean (SD))*†	173 (9.99)	173 (9.99)	173 (9.96)	172.52 (9.92)	172.50 (9.91)	172.61 (9.96)	1.1
Weight (mean (SD))*†	80 (16.13)	80 (16.15)	80 (15.86)	80.02 (16.30)	80.04 (16.40)	79.95 (15.86)	1.1
BMI (mean (SD))*†	27 (4.71)	27 (4.72)	27 (4.60)	27 (4.75)	27 (4.78)	27 (4.61)	1.2
Chest pain category (%)**†							56.4
Non-anginal	8198 (56.8)	7723 (58.5)	475 (39.0)	1965 (36.7)	1490 (36.1)	475 (39.1)	
Atypical	2092 (14.5)	1906 (14.4)	186 (15.3)	861 (16.1)	675 (16.3)	186 (15.3)	
Typical	4131 (28.6)	3574 (27.1)	557 (45.7)	2521 (47.1)	1967 (47.6)	554 (45.6)	
Smoking status (%)**†							6.3
Current	13 050 (42.1)	12 285 (42.6)	765 (35.5)	4067 (35.0)	3303 (34.9)	764 (35.5)	
Former	9907 (32.0)	9156 (31.7)	751 (34.9)	4091 (35.2)	3342 (35.3)	749 (34.8)	
Never	8041 (25.9)	7404 (25.7)	637 (29.6)	3456 (29.8)	2819 (29.8)	637 (29.6)	
Family history of atherosclerosis (%)**†	11 644 (35.2)	10 593 (34.4)	1051 (45.5)	5662 (45.1)	4615 (45.1)	1047 (45.4)	0.0
Consult year (%)**†							0.0
2007–2010	4344 (13.1)	4319 (14.0)	25 (1.1)	133 (1.1)	108 (1.1)	25 (1.1)	
2011–2014	14 362 (43.4)	13 234 (43.0)	1128 (48.8)	6025 (48.0)	4900 (47.9)	1125 (48.7)	
2015–2018	14 362 (43.4)	13 203 (42.9)	1159 (50.1)	6387 (50.9)	5229 (51.1)	1158 (50.2)	
Diagnosis of CHD at baseline (%)**†	2731 (8.3)	2612 (8.5)	119 (5.1)	659 (5.3)	540 (5.3)	119 (5.2)	0.0
Diagnosis of cerebrovascular disease at baseline (%)**†	975 (2.9)	918 (3.0)	57 (2.5)	303 (2.4)	246 (2.4)	57 (2.5)	0.0
Medication prescribed at baseline, n (%)							
Aspirin**†	1209 (3.7)	1130 (3.7)	79 (3.4)	442 (3.5)	363 (3.5)	79 (3.4)	0.0
Beta-blocker**†	1266 (3.8)	1171 (3.8)	95 (4.1)	537 (4.3)	442 (4.3)	95 (4.1)	0.0
Calcium channel blocker**†	608 (1.8)	572 (1.9)	36 (1.6)	184 (1.5)	148 (1.4)	36 (1.6)	0.0
Nitrate**†	522 (1.6)	498 (1.6)	24 (1.0)	124 (1.0)	100 (1.0)	24 (1.0)	0.0
Statin**†	1335 (4.0)	1259 (4.1)	76 (3.3)	415 (3.3)	339 (3.3)	76 (3.3)	0.0
Conclusion of exercise test (%)**†							17.7
Abnormal	2295 (8.4)	1949 (7.7)	346 (18.7)	1570 (15.6)	1227 (15.0)	343 (18.6)	
Inconclusive	5622 (20.7)	5113 (20.2)	509 (27.5)	2960 (29.5)	2452 (29.9)	508 (27.5)	
Normal	19 308 (70.9)	18 311 (72.2)	997 (53.8)	5518 (54.9)	4521 (55.1)	997 (54.0)	
Domestic region in the NL (%)**†							0.0
Middle	13 991 (42.3)	12 693 (41.3)	1298 (56.1)	7103 (56.6)	5809 (56.7)	1294 (56.1)	
North	17 339 (52.4)	16 344 (53.1)	995 (43.0)	5332 (42.5)	4337 (42.4)	995 (43.1)	

Continued

Table 1 Continued

	Original sample		Matched sample		Missing		
	Overall	Patients without a CT-first strategy	Overall	CT-first	Patients without a CT-first strategy	CT-first	%
South	1738 (5.3)	1719 (5.6)	110 (0.9)	19 (0.8)	91 (0.9)	19 (0.8)	
Total cholesterol in mmol/L (mean (SD))*†	5.15 (1.13)	5.13 (1.13)	5.32 (1.16)	5.33 (1.17)	5.31 (1.16)	5.33 (1.16)	24.4
10-year HeartSCORE in % (median (IQR))	1.75(0.47, 4.97)	1.73(0.44, 5.03)	2.04(0.60, 5.45)	1.92(0.75, 4.46)	2.08(0.57, 5.67)	1.91(0.75, 4.47)	30.9
Pretest probability (median (IQR))	10 (3–22)	10 (3–22)	13.00 (6.00–26.00)	13 (6–22)	13.00 (6.00–22.00)	13.00 (6.00–22.00)	61.8
Pretest probability of CAD in %, n (%)							61.8
High >15%	4412 (34.9)	3939 (34.2)	2128 (45.0)	473 (41.7)	1657 (46.0)	471 (41.6)	
Intermediate 5%–15%	4028 (31.9)	3600 (31.3)	1512 (31.9)	428 (37.7)	1085 (30.1)	427 (37.8)	
Low <5%	4199 (33.2)	3966 (34.5)	1093 (23.1)	233 (20.5)	860 (23.9)	233 (20.6)	
All-cause mortality (%)*	1331 (4.0)	1288 (4.2)	406 (3.2)	43 (1.9)	363 (3.5)	43 (1.9)	0.0
Cardiovascular mortality (%)	329 (1.0)	313 (1.0)	111 (0.9)	16 (0.7)	95 (0.9)	16 (0.7)	0.0
Follow-up in years (median (IQR))	5.5 (3.4–7.8)	5.6 (3.4–7.9)	4.9 (3.2–6.7)	5.1 (3.3–6.9)	4.9 (3.2–6.7)	5.1 (3.3–6.8)	0.0
Nelson-Aalen estimator* (median (IQR))	0.0348 (0.0189–0.0579)	0.0354 (0.0188–0.0594)	0.0302 (0.0181–0.0463)	0.0313 (0.0187–0.0472)	0.0301 (0.0179–0.0460)	0.0312 (0.0187–0.0472)	

Baseline table representing the distribution of baseline variables before and after matching on the PS. Pretest probability is derived from the 2019, ESC Guidelines.^{12,24} The summary statistics are shown as the data before imputation. Missing are the percentage of missing observations in the total population.

*Variables used for multiple imputation.
†Variables used for calculation of PS.

BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; ESC, European Society of Cardiology; PS, propensity score.

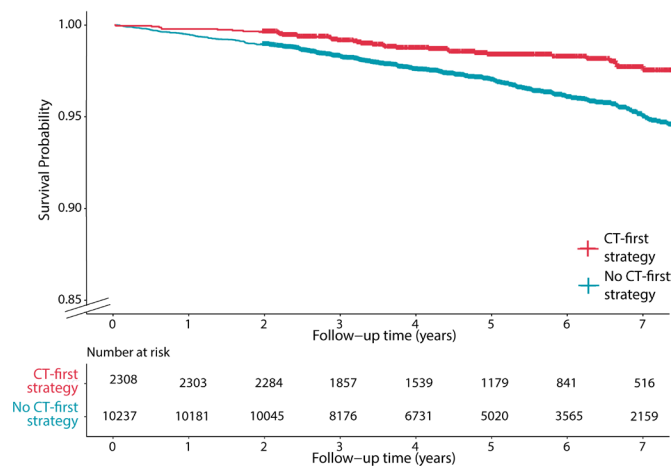


Figure 2 Kaplan-Meier curves for all-cause mortality of the CT-first and the without a CT-first study population.

were filled with a negative family history. Included variables for multiple imputation models are indicated in table 1.

PS matching

PS matching²¹ was used to ensure a comparable sample between patients with and without a CT-first strategy. PSs were calculated for each patient separately in each imputed dataset with a logistic regression model including 19 variables, as indicated in table 1. This selection of variables was based on clinically relevant variables and baseline differences between both groups. Thereafter, the average PS of the imputation datasets was calculated for each patient. We matched five patients who did not receive a CT-first strategy to one patient with a CT-first strategy based on the calculated PSs per patient using the nearest neighbour method with a calliper width of 0.05 and no replacement (R-package: *matchit*,²² V.3.0.2). Comparability of the groups after matching was assessed by inspection of the balance of baseline variables. The selected patient population is further referred to as the matched sample.

Statistical analysis

Descriptive statistics are presented as mean with SD or median with IQR, where appropriate, for continuous variables and counts and percentages for categorical variables. All-cause and cardiovascular mortality were analysed with Kaplan-Meier curves and Cox regression models on the matched patient selection. Other secondary outcomes were compared with χ^2 testing.

Subgroup analyses were performed for type of chest pain (anginal/non-anginal), sex (men/women), age (<65 years/ \geq 65 years), Systematic COronary Risk Evaluation (SCORE) (<5%/ \geq 5%)²³ and pretest probability of CAD (<5%/ \geq 5%).²⁴ The p value for interaction was determined for each analysis. Outcome for all subgroup analyses was all-cause mortality.

Sensitivity analyses were done to evaluate the effect of patient’s residency and inclusion year. In these analyses, a Cox regression for all-cause mortality was performed. Another sensitivity analysis excluded all patients referred to one specific diagnostic centre, only performing CCTA in case of medical need or if calcium score was above 0. As no information of the centre that was visited is available in the database, residency of the patient is used as a substitute. A final sensitivity analysis removed all patients without a CT but with CAG to evaluate the effect on the

results. These sensitivity analyses evaluated Cox regressions for both cardiovascular and all-cause mortality.

All data analyses were done with R (V.3.6.2) and RStudio (V.1.1.463).

Patient and public involvement

Patients were not involved in any stage of this research process.

RESULTS

Study population

A total of 34311 patients with chest pain met the inclusion criteria and were selected from the CCN database (figure 1). After linking with the database of Statistics Netherlands, mortality data of 33068 (96.4%) patients were available. This selection included 2312 and 30756 patients, respectively, with and without a CT-first strategy.

Mean age of the included patients (n=33068) was 56 years and 53.3% were women. Before PS matching, patients in the CT-first group (table 1) were older (57 vs 55 years), less likely to be current smokers (35.5% vs 42.6%) and had a higher incidence of typical chest pain (45.7% vs 27.1%). Yet, the presence of comorbidities was comparable. Median follow-up was 5.5 (IQR: 3.4–7.8) years, and 1331 (4.0%) patients died during follow-up. In 329 (1.0%) patients, a cardiovascular cause of death was assigned. Thus, PSs were distributed differently between patients with and without a CT-first strategy (online supplemental figure 1).

After PS matching, 2308 patients were in the CT-first group, and 10237 patients were matched to this group. Patients in the CT-first group had a median coronary artery calcification score of 2.20 (IQR: 0–88). There were 871, 329 and 225 filed stenoses in the left anterior descending artery, right coronary artery and circumflex artery, respectively, of which 489 (34.3%) were reported to be significant (>50% stenosis). In the matched sample, baseline characteristics were more equally distributed as compared with the unmatched sample (table 1), for example, mean age (57 years in both groups) and type of chest pain (non-anginal 39.1% vs 36.1%, atypical 15.3% vs 16.3%, and typical 45.6% vs 47.6% for, respectively, with and without a CT-first strategy). Consequently, the distribution of the PS of the included patients showed improved overlap in the matched sample (online supplemental figure 1). The matched sample (n=12545) was used for the analyses of primary and secondary outcomes.

Outcome analysis

All-cause and cardiovascular mortality after PS matching

In the matched sample 406 (3.2%) patients died. In 111 (0.9%) patients, there was a cardiovascular cause of death. Median follow-up was 4.9 years. In patients with a CT-first strategy, all-cause mortality was 1.9% (n=43) compared with 3.5% (n=363) in patients without a CT-first strategy (HR: 0.51, 95% CI 0.37 to 0.70). The Kaplan-Meier curves for patients with and without a CT-first strategy are shown in figure 2 and show a consistent divergent pattern over up to 7 years of follow-up. Cardiovascular mortality for patients in the CT-first group was 16 (0.7%) and 95 (0.9%) for the patients without a CT-first strategy, respectively. The corresponding HR for cardiovascular mortality was 0.73 (95% CI 0.43 to 1.24). The corresponding Kaplan-Meier curves are shown in online supplemental figure 2.

Downstream diagnostics and interventions

A total of 3432 (27.4%) patients of the matched cohort had diagnostic or therapeutic follow-up. The percentage of CAGs (16.2% vs 10.6%, p<0.001) and coronary interventions (8.5% vs 5.7%, p<0.001) were higher in the CT-first strategy group, compared with the group of patients without CT (table 2). The same was seen for the number of stress ECGs, which was higher for CT-first patients (17.5% vs 15.6%, p=0.03), yet the time interval between initial presentation and stress ECG was shorter in patients without a CT-first strategy (median time between chest pain consult and stress ECG: 112 days, IQR: 25–598, vs 301 days, IQR: 91–759). Follow-up cardiac perfusion imaging did not show any differences (3.0% vs 2.8% in, respectively, patients with and without a CT-first strategy).

Medication use

Medication use for primary or secondary prevention of CAD (including aspirin, statins, beta-blockers, calcium channel blockers and nitrates) at baseline was similar for patients with and without a CT-first strategy (tables 1 and 3). After initial chest pain consult, initiation of aspirin (44.9% vs 27.1%, p<0.001), b-blockers (37.8% vs 25.5%, p<0.001) and statins (48.7% vs 30.3%, p<0.001) was higher in the CT-first strategy group, compared with the group without CT.

Table 2 Distribution of diagnostics and therapeutics during follow-up

	CT-first (n=2308)	Patients without a CT-first strategy (n=10237)	P value
Anatomical imaging (%)	392 (17.0)	1435 (14.0)	<0.001
Perfusion imaging (%)	70 (3.0)	290 (2.8)	0.652
Coronary interventions (%)	197 (8.5)	581 (5.7)	<0.001
Stress ECG at CCN (%)	403 (17.5)	1600 (15.6)	0.032
Coronary angiography (%)	373 (16.2)	1086 (10.6)	<0.001
Cardiac CT (%)	23 (1.0)	429 (4.2)	<0.001
Time (days) between chest pain consult – stress ECG (median (IQR))	301.00 (91.00–759.00)	112.00 (25.00–597.75)	<0.001
Time (days) between chest pain consult – anatomical imaging (median (IQR))	57.00 (37.75–87.25)	49.00 (20.00–119.50)	<0.001
Time (days) between chest pain consult – perfusion imaging (median (IQR))	74.00 (49.25–162.25)	36.50 (17.00–91.00)	<0.001
Time (days) between chest pain consult – coronary intervention (median (IQR))	65.00 (42.00–98.00)	51.00 (21.00–102.00)	<0.001

Distribution of diagnostics and therapeutics during follow-up in patients with a CT-first strategy and the population without a CT-first strategy. Anatomical imaging comprises cardiac CT and coronary angiography. Perfusion imaging includes cardiac PET, SPECT and MRI. Coronary interventions are coronary artery bypass grafts and percutaneous coronary interventions.

CCN, Cardiology Centers of the Netherlands; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Table 3 Medication use in selected population

	CT-first (n=2308)	Patients without a CT-first strategy (n=10237)
Aspirin (%)		
Continued	57 (2.5)	323 (3.2)
Discontinued	22 (1.0)	40 (0.4)
Initiated	1036 (44.9)	2770 (27.1)
Initiated and discontinued	339 (14.7)	369 (3.6)
Beta-blocker (%)		
Continued	75 (3.2)	419 (4.1)
Discontinued	20 (0.9)	23 (0.2)
Initiated	873 (37.8)	2611 (25.5)
Initiated and discontinued	549 (23.8)	525 (5.1)
Calcium-channel blocker (%)		
Continued	36 (1.6)	135 (1.3)
Discontinued	<10 (<0.4)	13 (0.1)
Initiated	287 (12.4)	1311 (12.8)
Initiated and discontinued	81 (3.5)	213 (2.1)
Nitrates (%)		
Continued	18 (0.8)	92 (0.9)
Discontinued	<10 (<0.4)	<10 (<0.1)
Initiated	502 (21.8)	1791 (17.5)
Initiated and discontinued	165 (7.1)	260 (2.5)
Statins (%)		
Continued	71 (3.1)	332 (3.2)
Discontinued	<10 (<0.4)	<10 (<0.1)
Initiated	1125 (48.7)	3102 (30.3)
Initiated and discontinued	84 (3.6)	141 (1.4)

Medication use in selected patients for the CT-first strategy and patients without a CT-first strategy. Continued medication is defined as medication that was started before the chest pain consult and continued for at least 120 following days. Discontinued medication is medication started before the consult and stopped within 120 days. Initiated medication was started within the time frame from chest pain consult until 120 days after the consult. Initiated and discontinued medication was medication that was started and discontinued within 120 days following the chest pain consult.

Subgroup and sensitivity analyses

The association between having a cardiac CT for diagnostic evaluation of chest pain and all-cause mortality was further investigated in clinically relevant subgroups (figure 3). Men showed greater benefit from a CT-first strategy with respect to all-cause mortality, although p value for interaction was not significant. This p-value was only significant for type of chest pain (p-value:

0.013) and risk of CAD (p-value: 0.0046), implying that patients with a possible anginal origin of chest pain and with an intermediate to high risk of CAD benefit from a CT-first strategy.

Sensitivity analyses showed that HRs were similar for the different regions of the Netherlands and for the inclusion year of patients (online supplemental table 1). Residence and inclusion year were taken into account during the PS calculation. This suggests a similar distribution of these variables in the CT-first and without CT-first group. Sensitivity analysis of removal of patients (n=4883) from one centre that did not structurally perform cardiac CT including calcium scoring and CCTA showed comparable HR for all-cause mortality (0.44, 95% CI 0.28 to 0.67 vs 0.51, 95% CI 0.37 to 0.70) and HR for cardiovascular mortality (0.70, 95% CI 0.37 to 1.33 vs 0.73 95% CI 0.43 to 1.23) to the main matched sample. After removal of all patients with CAG within 10 weeks after their initial visit (n=959), the HR for all-cause mortality (0.54, 95% CI 0.39 to 0.74) and cardiovascular mortality (0.78, 95% CI 0.45 to 1.34) changed but within CIs.

DISCUSSION

The analysis performed in this study demonstrated that upstream inclusion of cardiac CT in diagnostic work-up of patients with chest pain was associated with a significant lowering of all-cause mortality, irrespective of the outcome of the cardiac CT. We also observed a lower cardiovascular mortality rate in CT-first patients, although this difference was not statistically significant. This can be due to the low numbers of a cardiovascular cause of deaths and insufficient registration of the cause of death. Our data also show that patients with a CT-first strategy had more downstream therapeutics and diagnostic testing. This is in accordance with findings from other registries.¹⁰ The presented results underscore and complement the prominent role of cardiac CT in the diagnostic work-up of patients presenting with chest pain in clinical guidelines,¹² which has also been internationally addressed.²⁵

Based on previous publications, it is assumed that patients that undergo cardiac CT in addition to regular care receive an accurate diagnosis earlier and more often,²⁶ after which targeted antianginal and preventative therapy is initiated, resulting in overall superior survival in these patients.^{27,28} The prescription

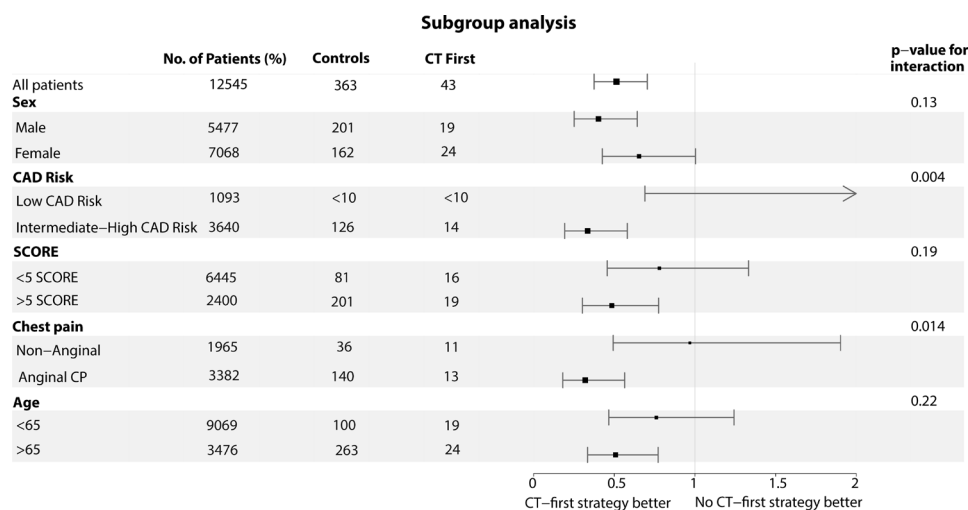


Figure 3 Forest plot of the subgroup analysis. CAD risk is defined as the pretest probability of CAD according to the ESC guidelines of 2019: Low : <5%, intermediate to high: >5%. Anginal chest pain includes typical and atypical chest pain. SCORE is the cardiovascular risk score as defined by the Systematic COronary Risk Evaluation. CAD, coronary artery disease; ESC, European Society of Cardiology.

of preventative medication, especially statins, aspirin and beta blockers to patients with CT-verified atherosclerotic lesions was thought to be the major reason for lower mortality rates observed in patients undergoing cardiac CT in the SCOT-HEART trial. However, cardiovascular mortality rates were not significantly lower in the CT-first population. One reason for the lower risk of all-cause mortality could be the identification of relevant extracardiac findings, which occur in approximately 3%. Of these, pulmonary nodules make up the largest share (1.3%).²⁹ Also the inclusion of patients at lower risk for CAD in the CT-first group that have not been properly identified due to missing values might account for the discrepancy in all-cause and cardiovascular mortality after a CT-first strategy. Finally, the number of events and follow-up time might be too low to establish the effect of lifestyle changes as a result of the visualisation of coronaries on CT. Yet, as we did not include an in-depth analysis of the results of cardiac CT, we could not relate this to the presence of CAD or atherosclerotic lesions.

In accordance with the SCOT-HEART trial, we observed a higher referral rate for follow-up diagnostics and interventions in CT-first patients.^{5, 27} We did not perform analyses of these downstream costs. Therefore, no statements can be given about the cost-to-benefit ratio in patients with and without a cardiac CT-first strategy. Yet, in the light of a faster and more often correct diagnosis,²⁷ lower cumulative diagnostic expenses could be expected for patients with a cardiac CT.²⁶ Nevertheless, cost-effectiveness of the CT-first strategy needs to be established and should take into account the higher number of revascularisations and medication prescriptions in CT-first patients.^{10, 30} On the contrary, the relatively low cost and wide availability of CT makes it accessible for more patients compared with other cardiac imaging strategies.

Strengths and limitations

The presented study has multiple strengths. First, the use of EHR data aids to address concerns of health volunteer bias and under-representation of patient subgroups that are mostly seen in clinical trials. This is represented in the large study population and equal distribution of sex within the population. Thus, the included population is an actual representation of the population that the guidelines are intended for. Therefore, the results have high external validity. Second, the longer follow-up in this study has incremental value compared with the Danish nationwide registry¹⁰ and the PROMISE trial⁸ that presented data with a follow-up of respectively 3.6 years and 25 months.

The study was limited by the lack of information on cardiovascular events, including cardiovascular hospitalisations, which hampered the analysis of these events. Another limitation of regular care data is confounding by indication; patients with a higher pretest probability of CAD are more likely to be referred for cardiac CT than patients with a lower pretest probability. To avoid this potential bias, PS matching was used to ensure comparability between patients with and without a CT-first strategy. Regardless, one would have expected that patients with a higher pretest likelihood would show lower survival. Yet, we observed the opposite, vindicating that baseline differences between both groups were properly accounted for. Nonetheless, it is impossible to eliminate or to take into account the influence of unmeasured confounders or instrumental variables in the presented methodology.

To conclude, this study was the first to demonstrate a significantly lower HR for all-cause mortality in patients with chest pain who had a CT-first strategy compared with patients who

did not have a CT-first strategy. It is hypothesised that patients with a CT-first strategy obtain a more tailored therapy, including risk-reducing medication. These results support a CT-first strategy for patients with chest pain and strengthen the prominent role for cardiac CT as the primary method for diagnostic work-up of patients with chest pain, as suggested by the current ESC guidelines.

Key messages

What is already known on this subject?

⇒ Upstream incorporation of cardiac CT in the diagnostic pathway (CT-first strategy) has shown to reduce fatal and non-fatal myocardial infarction with 50% in patients with chest pain in the SCOT-HEART study. Although registry studies and the PROMISE trial could not confirm these findings, international guidelines have incorporated a CT-first strategy in the evaluation of patients with chest pain. Regular care data can aid in building the evidence for this guideline implementation.

What might this study add?

⇒ A CT-first strategy in patients with chest pain is associated with a lower risk of all-cause mortality (HR: 0.51, 95% CI 0.37 to 0.70), but not cardiovascular mortality (HR: 0.73, 95% CI 0.43 to 1.24). In patients with a CT-first strategy, prescriptions of risk-reducing and antianginal medication were higher compared with patients without a CT-first strategy.
⇒ Propensity score matching and multiple imputation can reduce bias present in regular care data. These methods enable researchers to use the potential of regular care data to strengthen the evidence base for clinical practices.

How might this impact on clinical practice?

⇒ Patients undergoing a cardiac CT as part of their diagnostic work-up for chest pain might have increased survival, compared with patients undergoing usual care. It is hypothesised this is due to more timely and accurate diagnosis of the origin of chest pain, resulting in targeted therapeutics and initiation of antianginal and preventative medication.

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Competing interests LH, IIT and GAS are employed by Cardiology Centres of the Netherlands.

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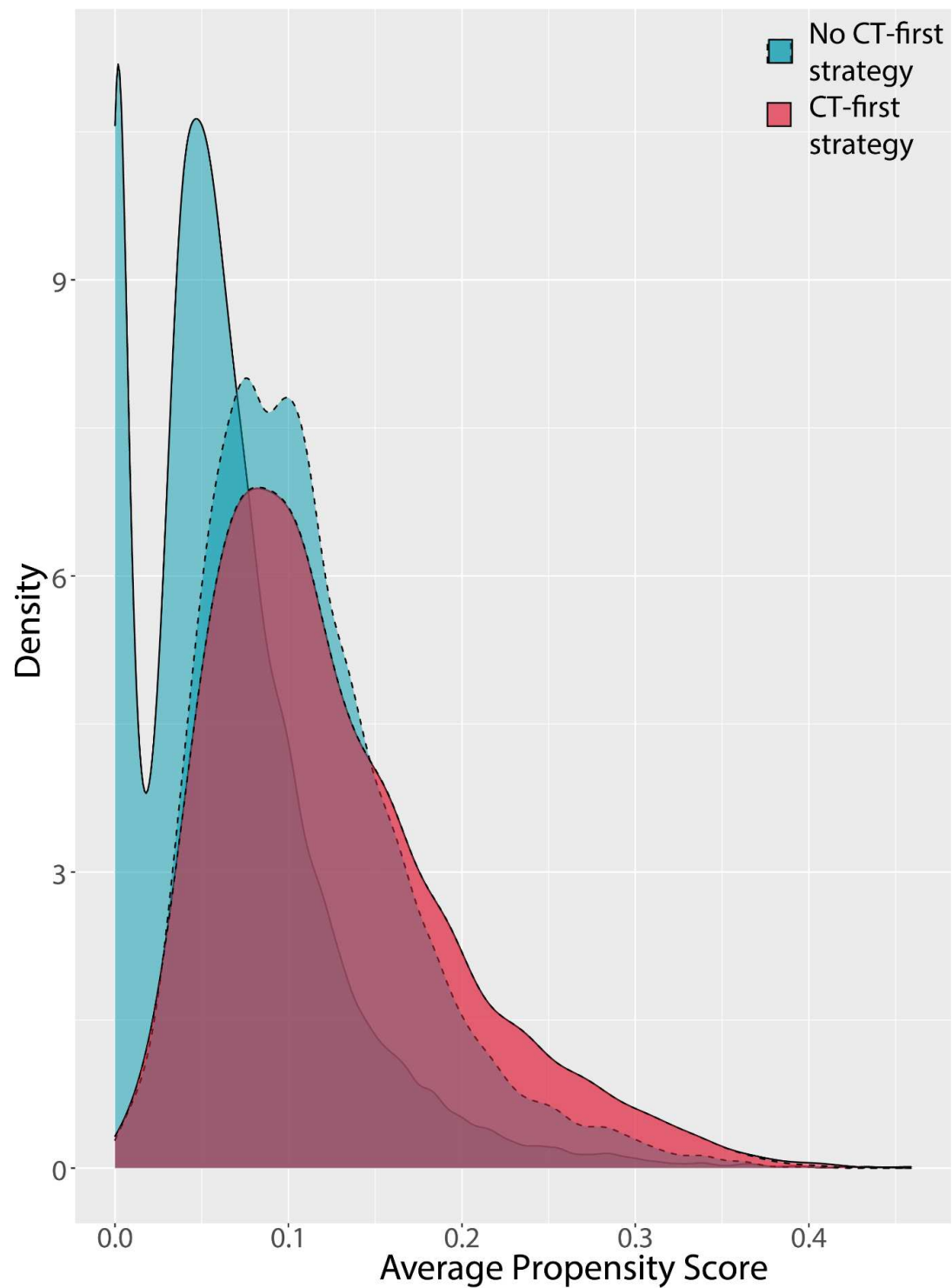
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Supplemental files

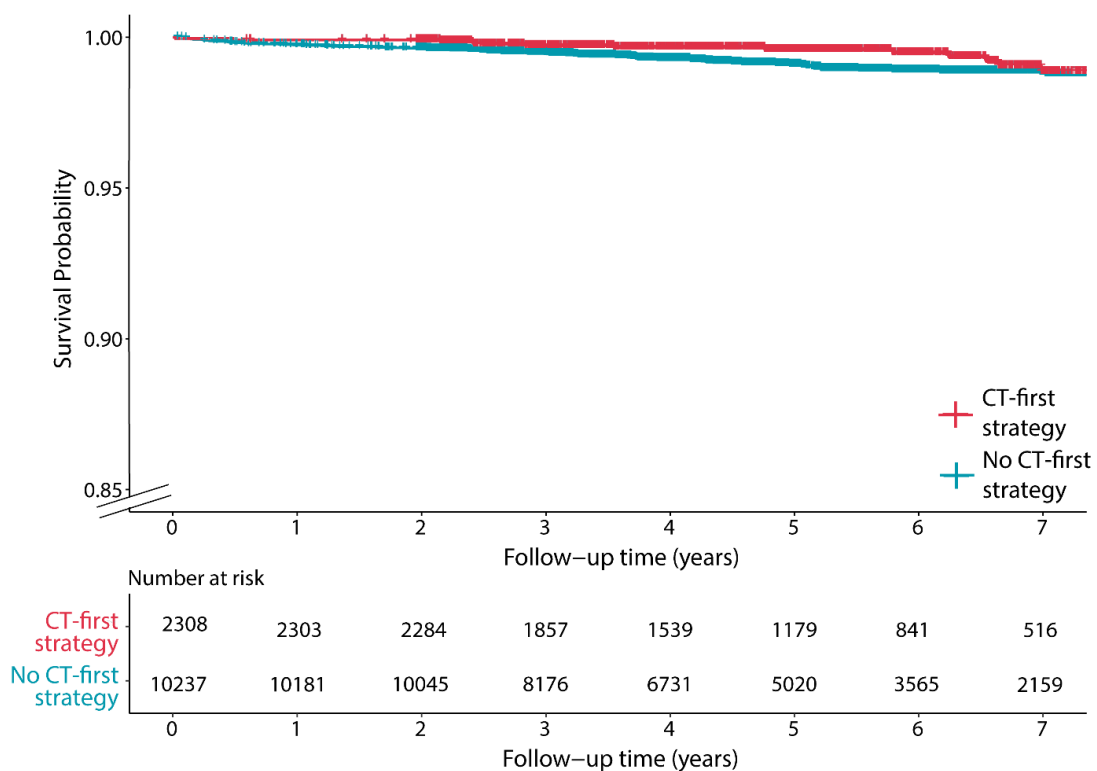
Supplementary table 1 - Results of sensitivity analyses

	Number of patients	Without CT-first strategy	CT-first strategy	Events in patients without CT-first strategy	Events in patients with CT-first strategy	Hazard ratio all-cause mortality [95%-CI]
All patients	12545	10237	2308	363	43	0.51 [0.37-0.70]
North	5332	4337	995	154	14	0.39 [0.23-0.68]
Middle	7103	5809	1294	206	29	0.60 [0.40-0.88]
South	110	91	19	<10	<10	NA
2007-2010	133	108	25	<10	<10	2.18 [0.39-11.9]
2011-2014	6025	4900	1125	257	30	0.49 [0.34-0.72]
2015-2018	6387	5229	1158	102	11	0.48 [0.25-0.89]

This table shows the results of the cox regression analysis for all-cause mortality for patient's residence of different regions of the Netherlands and for the inclusion year of the patient. 'North' includes Friesland, Groningen, Drenthe, Overijssel, Flevoland and North-Holland, 'Middle' includes Zuid-Holland, Utrecht and Gelderland, 'South' includes Zeeland, Noord-Brabant and Limburg.



Supplementary figure 1 - Distribution of the propensity score in the CT-first patients and patients without a CT-first strategy before (solid) and after (dashed) propensity score matching.



Supplementary figure 2 - Kaplan-Meier curves for cardiovascular mortality of the CT-first and the without a CT-first study population.