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Non contrast cardiac CT scan as a risk stratification tool in non-specific chest pain patients

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Abstract

Objectives: To examine the prevalence of coronary artery calcification and frequency of cardiac events in a cohort of non-specific chest pain (NSCP) patients (an acute admission for chest pain and discharged without an obvious reason for the chest pain) and compare with the background population.
Design: A double blinded prospective cohort study examined with non-contrast CT scan and measurement of the CAC score.
Setting: Departments of Emergency and Cardiology in the Southern Region of Denmark.
Subjects: The study population consists of 229 NSCP patients and was compared with 722 patients from the background population. The patients were included from September 2014 until June 2015 and followed for a year.
Main outcomes measures: Prevalence of CAC. Cardiac related mortality, acute myocardial infarction, unstable angina and coronary revascularisation.
Results: No significant difference in prevalence of CAC was found. During one year follow-up two (0.9%) NSCP patients were revascularised, while no one died experienced MI, VT or had UAP. In the background population four (0.6%) experienced a clinical endpoint; one cardiac related death, two with MI, one had VT.
Conclusion: The prevalence of CAC is comparable with the background population, and the prognosis for NSCP patients during one year follow up is excellent.

Keywords: Coronary heart disease, ischemic heart disease, myocardial infarction, cardiovascular imaging, computed tomography.

Strength and limitation

- Patients included from multiple centers
- Outcome data from well documented and validated registers
- Selected patient cohort and age
- Definitions of risk factors differed between the cohort
- Data gathering differed for the main study population and the background population for comparison.

Introduction

Cardio vascular disease (CVD) remains a major public health problem and causes half of all deaths in Europe, while coronary artery disease (CAD) accounts for 20% of all deaths in Europe(1). One of five patients with chest pain in the emergency departments turns out to fulfill the diagnostic criteria of acute myocardial infarction (MI) (2, 3). Other causes of acute chest pain may be of cardiovascular origin (aneurism, aortic dissection pulmonary embolism), but can also be non-cardiac related (gastrointestinal disorders, musculoskeletal disorders) while a significant number of patients the cause of symptoms remains unknown, and these patients are defined as having non-Specific Chest Pain (NSCP).

However, even if acute MI is definitely excluded, CAD may be present with an inherent risk of future cardiac events. Hence, 0.8% of NSCP patients experienced an adverse outcome during 30 days follows up after discharge from an emergency department (4). It has been shown that up to 20% of patients with CAD do not have any traditional risk factors such as hypertension, hyperlipidemia, diabetes or smoking (5), thus a non-contrast cardiac CT might serve as a tool in risk stratification by measuring the presence and extent of coronary artery calcification (CAC). The advantages of non-contrast cardiac CT are that the method is easy to perform and interpret, the reproducibility is high and the radiation exposure is low (3, 6-8). The role of a non-contrast cardiac CT as a risk stratification tool has been established in asymptomatic persons (9) . The prevalence of CAC in an asymptomatic general population without known prior CVD has been shown to be 44%-50% (10, 11). The Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that an increased CAC score was associated with a higher risk of CAD during a 10 year follow up period (12). However, the clinical importance of CAC in patients with acute chest pain, in whom an acute MI has been ruled out, remains to be investigated.

In order to evaluate the non-contrast cardiac CT as a potential risk stratification tool for patients with NSCP the aim of the present study was twofold. First, we wanted to investigate the prevalence of CAC among NSCP patients and to compare the findings with observations from an asymptomatic background population. Second, we wished to examine the frequency of clinical cardiac events related to CAC in NSCP patients during a 12 months follow-up period, and compare these data with the results from the asymptomatic background population but also those directly referred for a further cardiac test from index contact.

Method and materials

Study design

This study was a double blinded prospective cohort study including patients from the Emergency and Cardiology Departments in the region of Southern Denmark. All patients with an acute visit for chest pain to the hospitals in Odense, Svendborg, Vejle, Kolding, Aabenraa or Sonderborg, and at least one troponin measurement during the contact were included. The inclusion period was from September 2014 until May 2015. The patients were invited for this study, if they were discharged without any obvious reason for the chest pain (NSCP diagnosis (ICD codes: DR072/DR073/DR034/DR035)).

Study population

Through the central biochemical laboratory for all hospitals in the region of Southern Denmark all patients with measurement of troponin in the Emergency and Cardiology Departments were identified on a daily basis. Electronic patient files were scrutinized in all patients with normal troponin values, as defined below. Patients had to complete a structured questionnaire by a telephone interview within three days of discharge from the index admission.

Afterwards written information and a consent form for participation was sent to the patient. Patients who returned the consent form were scheduled for the CT scan. The participant and the physicians were blinded for the result of the non-contrast CT.

The inclusion and exclusion criteria for the study is defined below

Inclusion criteria:

- Normal troponin (troponin T <14 ng/mL or troponin I< 30 ng/mL)'
- Age 30-70 years

- Known with one risk factor for CAD (hypertension, hypercholesterolemia, familiar disposition, and diabetes mellitus, present or former smoker).

Exclusions criteria:

- Living outside the catchment area of Region of Southern Denmark
- Refusing participation in the telephone interview and or CT scan
- Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and cardiac imaging test within the last 5 years
- Not Danish speaking,

We used the Danish Risk Score study (DanRisk) population (11) as a control group representing the background population. The DanRisk study population consisted of 1 257 asymptomatic subjects aged 50 and 60 years old, who in 2009 had been examined in one of four cardiac CT centers (Odense, Esbjerg, Vejle or Svendborg) in the region of Southern Denmark. The inclusion criteria in this study were at least one risk factor for CAD (hypertension, hypercholesterolemia, familiar disposition, known smoker and diabetes mellitus), and exclusion criteria were known CAD. Patients missing CAC were excluded. The patient selection procedure used in the DanRisk study is described in details elsewhere (11).

Definitions

In the NSCP population comorbidity was self-reported. Diabetes Mellitus was defined as the use of antidiabetic medication or a diagnosis given by their general practitioner. Hypertension and hypercholesterolemia were present if the patients stated to be in relevant medical treatment or had received the diagnoses by the general practitioner. Family history was defined as a first degree relative with CVD without consideration of age. Smoking was defined as current smoker. Systolic and diastolic blood pressure and heart rate were retrieved from the patient files, as the first measured value during the index admission. Cholesterol values were collected up to 3 months before and 3 months after the index admission. The value closest to the index date was used. BMI was calculated based on self-reported height and weight.

For the DanRisk subjects in this study Diabetes Mellitus was defined as use of antidiabetic medication that included any oral antidiabetic drug and/or insulin. Hypertension was defined as the use of antihypertensive medical treatment. Antihypertensive therapy included angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonist, calcium channel blockers, diuretics, beta-blockers, alpha-blockers, and centrally active antihypertensive drugs. Hypercholesterolemia was defined as use of lipid lowering

medication. Family history was defined as first degree relative with CAD, male<55 years and female <65 years. Smoking was defined as current smoker. Blood pressure, heart rate, BMI and cholesterol values were measured at baseline examination.

Troponins

The troponin assays used for this study were high sensitive troponins with a 99th percentile upper reference limit.

The cardiac troponin I, used by Odense University Hospital, was analyzed by use of the Abbot Diagnostics architect with an upper reference limit of 99th percentile of 25 ng/L and a coefficient of variation < 10% at 5 ng/L. The decision limit for MI was set at >= 25 ng/L

Troponin T, used by all other participating hospitals, was analysed by Roche diagnostic elecsys 2010, modular analytics E170, Cobas e411, cobas e601. The 99th percentile upper reference limit was 14 ng/L and a coefficient variation <10% at 13 ng/L. The decision limit was set > 14 ng/L for MI.

Cardiac CT protocol

CAC was assessed by summing the scores from all foci in the coronary arteries and expressed in Agatston unit (AU)(reference til Agatston Score). CAC was assessed by trained radiographers, and reanalyzed by the first author. The correlation was 99%.

Two centers used dual-source CT scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany) with prospective ECG triggering. In persons with heart rate <75 beats/minute the ECG triggering was set in diastolic phase at 65-75% of the cardiac R-R interval. In persons with heart rate ≥75 beats/min the ECG triggering was set in systolic phase at 250-400 ms. Additional settings: slice thickness3 mm, collimation 128 x 0.6 mm, gantry rotation time 0.28ms, 120 kV tube voltage, 90mAs/rotation. One center used a GE 64-slice CT-scanner (Discovery 750 HD; GE Healthcare). In persons with heart rate <75 beats/minute the ECG triggering was set in diastolic phase at 75% of the cardiac R-R interval. In persons with heartrate ≥75 beats/min the ECG triggering was set in systolic phase at 40% of the cardiac R-R interval. Additional settings: slice thickness 2.5 mm, collimation 64 x 0.625 mm, gantry rotation time 0.35ms, 120 kV tube voltage and 200 mA tube current. The last center used a Toshiba Aquillion Next Generation CT scanner with prospective ECG triggering. If heart rate was <75 bpm the ECG triggering was in the diastole phase at 65%-75% of the R-R interval. In persons with heart rates ≥75 beats/min the ECG triggering was set in systolic phase at 40%. Slice Thickness was 0.5 mm, collimation after scan range 0.5 mm x 240 – 320, gantry rotation time 0.275 ms and 120 kV tube voltage.

Follow-up

The study was conducted as a double blinded study with a 12 month follow-up time. Neither the participants nor the investigators knew the results of the CAC score before the end of follow up. By then the participants and their general practitioner received a letter with the results of the CAC score.
The clinical endpoints in the follow-up study were cardiac death, ventricular tachycardia (VT), non-fatal MI, coronary revascularization and unstable angina. The endpoints were compared with DanRisk participants. Furthermore we did a comparison with NSCP patients who were referred for cardiac imaging testing at the index admission and thus did not participate in our study. These patients were referred for further diagnostic testing by the physician on call that evaluated these patients to have a higher risk of CAD.

Sample size

A sample size calculation was performed based on the prevalence of elevated CAC score (CAC>0 AU), and we knew that 44% of the general population represented by DanRisk had coronary calcifications (CAC>0 AU)(11). In a symptomatic population referred for coronary angiography 79% had a CAC>0 AU (13). We assumed in a symptomatic low risk population, the NSCP group, 62% would have CAC>0 AU. Confidence interval was set to 95%, and with an expected power of 80% using the Fleiss method gave us a sample size of 238 patients.

Statistical analyses

Categorical variables were presented with frequency tables and percentages, and continuous variables with mean and medians. Fischers exact test and Chi square test were used for categorical variables. The t-test was used for comparison of normally distributed variables, while the Wilcoxon's rank sum test was used for not normally distributed continuous variables. Odds ratio was calculated with multi-logistic regression.
Exclusion analyses (table 1) were performed between participants and non-participants. Non-participants were those who fulfilled the eligibility criteria but were not recruited. The variables were categorical variables and interferens was estimated with Fishers exact and chi square test. Age was non-parametric and reported with medians and interferens estimated with Wilcoxon's ranksum test.
Descriptive characteristics of the DanRisk and the NSCP patients (table 2) compromised categorical and continuous variable. The characteristics were reported with frequency and means. Statistics estimates were conducted with Fishers exact test and Chi square test for categorical and t-test for continuous variables.
The amount of CAC and its association with risk factors were reported with medians for each risk factor in NSCP patients and the DanRisk patients (table 3). P values estimates are based on Wilcoxon's ranksum test.

Comparison between coronary calcification (CAC>0 AU) in NSCP patients and the DanRisk population was performed with 2x2 tables and Chi square test, and the relationship between calcification in the NSCP and DanRisk patients adjusted for risk factors that were significant in table 2. Statistics were calculated by multivariate logistic regression on coronary calcification status (CAC=0 AU vs CAC >0 AU). The analyses were performed with STATA 14. A P-value <0.05 was considered to be significant.

Ethics

The protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20140055) and conducted in accordance with the Declaration of Helsinki. The study was registered in Clinical trial with number NCT02422316. The study was registered with The Danish Data Protection Agency (2008-58-0035 nr 1092). Written informed consent was obtained from each participant.
The DanRisk protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20080140) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Results

In total 4 289 patients aged 30 to 70 years old attended an Emergency or Cardiology Department and had at least one a troponin measurement done. After exclusion of 3 047 patients (i.e. elevated troponin, identified cause of the chest pain, no consent, see Figure 1), 1 241 were left for study eligibility. However, further 800 of these for different reasons (i.e. no risk factors, referred for coronary imaging) had to be excluded from participation in a cardiac CT scan examination. Of the remaining 441 patients with NSCP 229 patients (participants) accepted the invitation, and to undergo cardiac CT scan, while 212 patients (non-participants) either declined the invitation or did not show up at the time of cardiac CT-scan. The non-participants represented individuals that were eligible but not recruited. The mean age was 52 (IQR 44;60) and 57 (IQR 50;64)) years in participants and in non-participants, respectively, p=0.0.001. Significantly more were known with hypercholesterolemia and a family history of CVD among participants compared to non-participants. No significant difference was found in gender, diabetes, hypertension or smoking status. Table 1 lists the comparison between participants and non-participants.

Table 1 : Participants and non-participants comparison

	Participants		Non-participants		P-value*
	n=229	%	n=212	%	
Characteristics					
Median Age (years/IQR)	57(50-64)		52 (44-60)		0.001
Male	98	43	89	42	0.863
Diabetes mellitus	22	10	10	5	0.048
Hypertension	91	40	70	33	0.143
Hypercholesterolemia	97	42	67	32	0.020
Family history	124	54	93	44	0.031
Smoking	58	25	57	27	0.709

P values compares the proporiotions of participants and non-participants that are known with the specific variable

Figure 1: Flowchart for the inclusion of the NSCP population/ Figure 2: Flow chart for DanRisk

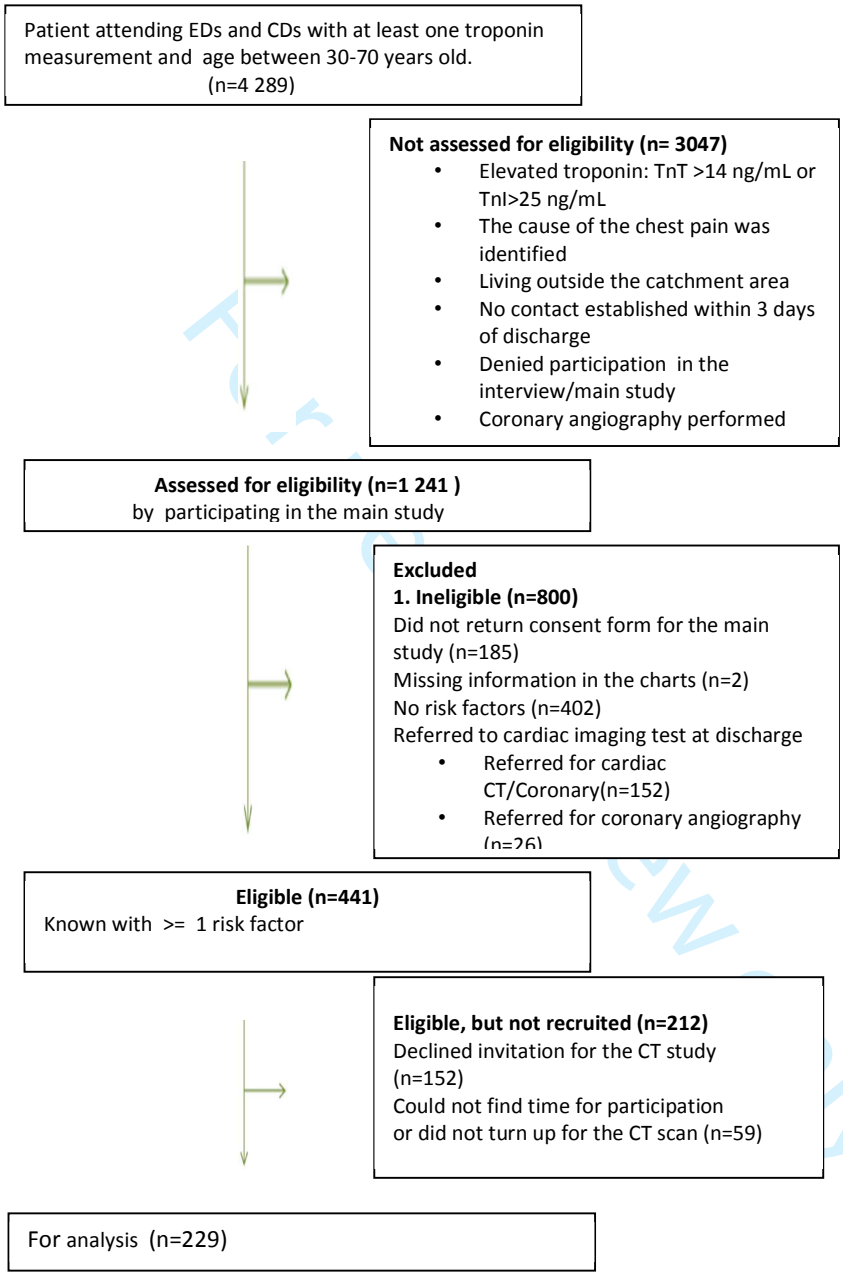

Figure 2 shows the inclusion of the patients in the DanRisk study. 1 825 random individuals 50 or 60 years old were invited for study participation. 1 257 accepted the invitation. In total 535 patients were excluded, 6 did not have a CAC score performed, 16 patients were known with CAD, and 513 did not fulfill the criteria of having at least one risk factor. In total 722 persons from the Danrisk study served as controls for NSCP patients.

Figure 2

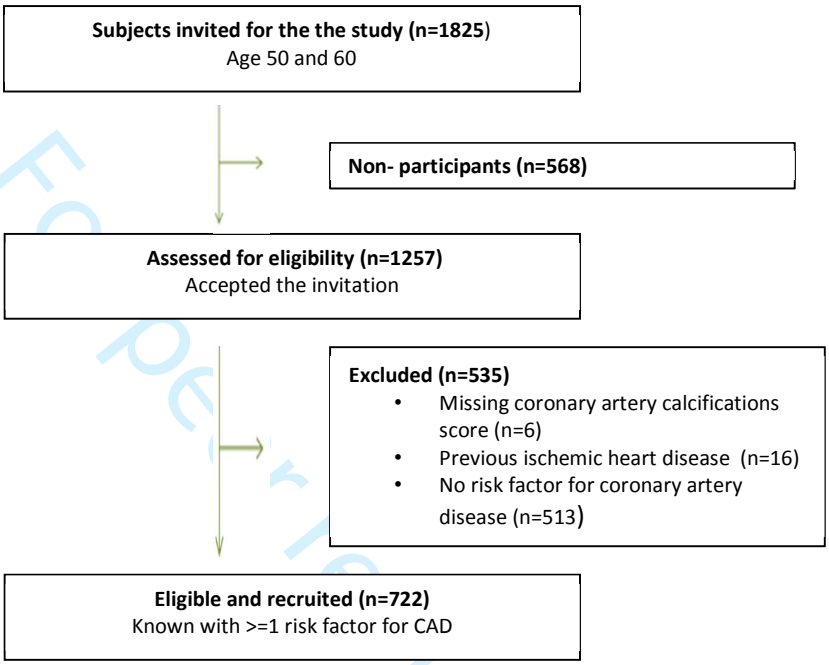

Table 2 lists the baseline characteristics for the NSCP patients and the DanRisk cohort. Mean age for the NSCP population was 57 years and 55 years for DanRisk patients (p=0.007). A significantly higher proportion of NSCP patients had known hypercholesterolemia and family history of IHD, while more participants in DanRisk were smoking. Furthermore, a significant difference between the populations regarding blood pressure, heart rate and total cholesterol was found.

Table 2: Descriptive characteristisc of NSCP and background population.

	NSCP population		Background population		P-value*
	n=229	%	n=722	%	
					0.476
Female	131	57	327	55	
Male	98	43	295	45	
Age					0.001
30-39	7	3	-		
40-49	46	20	-		
50-59	76	33	316	44	
60-70	100	44	406	56	
Hospital					0.001
Odense	70	31	175	24	
Vejle	63	27	171	24	
Aabenraa	58	25	-	-	
Svendborg	38	17	180	25	
Esbjerg	-	-	196	27	
Hypertension	91	40	266	37	0.458
Hypercholesterolemia	97	42	126	18	0.001
Diabetes	22	10	59	8	0.509
Family history	124	54	287	40	0.001
Smoking	58	25	314	44	0.001
	Mean		Mean		
Systolic blod pressure (mmhg)	144		137		0.001
Diastolic blod pressure (mmHg)	97		83		0.002
Pulse (rate/min)	74		71		0.001
Total cholesterol mmol/L	5.2		5.5		0.005
LDL cholesterol mmol/L	3.1		3.2		0.067
HDL cholesterolmmol/L	1.4		1.5		0.088
BMI (kg/m2)	27		27		0.715

*P values estimates for comparison of mean values.

The median CAC scores for each variable are listed in the Table 3. A significant difference was found between patients ≥ 60 years in the NSCP population and the 60 years old asymptomatic patients in in DanRisk cohort. Patients with hypertension in the NSCP population also had significantly more CAC than hypertensive DanRisk patients.

Table 3: Median CAC estimates based on characteristics variable

	NSCP Median CAC (IQR) AU	Background population Median CAC (IQR) AU	P-value*
Female	0(0;67)	0(0:18)	0.736
Male	18(0;83)	9(0;116)	0.117
Age			
30-39	0(0;1)		
40-49	0(0;5)		
50-59	0(0;33)	0(0;12.5)	0.247
60-70	47(0;147)	7(0;110)	0.008
Hospital			
Odense	0(0;26)	1(0;69)	0.019
Vejle	8(0;104)	4(0;28)	0.109
Aabenraa	10(0;120)	-	-
Svendborg	16(0;65)	0(0;61)	0.083
Esbjerg	-	0(0;66)	-
Hypertension	30(0;251)	4(0;96)	0.022
Hypercholesterolemia	6(0;94)	14(0;127)	0.878
Diabetes	61(0;253)	11(0;129)	0.251
Familiar history of CVD	3(0;72)	1(0;36)	0.198
Smoking	4(0;133)	5(0;73)	0.607

* P value compares median value of CAC (AU) between NSCP and background population.
AU=Agatston unit

The prevalence of CAC score >0 was 54 % in the NSCP population and 52 % in the DanRisk cohort (p=0.605). When adjusted for sex, age, hypercholesterolemia, smoking status and family history in a multilogistic regression analysis no significant difference was found between the presences of CAC in the NSCP population vs the DanRisk cohort (Odds ratio (OR) 1.3 (95%: 0.9-1.9), p=0.126).

During one year follow-up 2 out of 229 (0.9%) NSCP patients were revascularized, while no one died from cardiac related causes, or had a MI, VT or UAP. The two patients with events were a female aged 64 and a male aged 60 years with a CAC score of 349 and 2595, respectively. Both were known with hypertension, hypercholesterolemia and a family history of CVD. Fishers exact test showed no statistically difference in

endpoints p=0.636 between NSCP and DanRisk. The event rate in the DanRisk population was 4 /722 (0.6%) one cardiac related death, two had MI, and one had VT. All four patients were males. The patient with VT was 50 years, and had a CAC=0, but also a family history of CVD. The three other persons in the DanRisk cohort were 60 years old with a CAC score of 166, 832 and 1326 respectively. One was a smoker, one had hypertension and hypercholesterolemia, while the last was smoking, had diabetes and a family history of CVD

Table 4 : The distribution of CAC and endpoints for NSCP and background population.

	Total		CAC=0 AU		CAC>0 AU	
	n	%(CI)	n	%(CI)	n	%(CI)
NSCP	2/229	0.9(0.2-2.9)	0/106	0(0.0-3.0)	2/123	1.6(0.3-5.3)
Background population	4/722	0.6(0.2-1.3)	1/350	0.3(0.1-1.4)	3/372	0.8(0.2-2.2)

Table 4 shows how the clinical endpoints are associated with prevalence of CAC. No significant difference was found between the numbers of endpoints related to CAC between the groups.

211 patients were referred for further work up from the index contact and not included in this study. 152 went through a cardiac CT, 26 were referred for coronary angiography and 33 for myocardial perfusion scintigraphy. The combined clinical endpoints in this study were 11/211 (5.2%). Two patients had UAP, two had MI and 9 had coronary revascularization performed during one year of follow-up. No one had VT or died from cardiac related causes. Table 5 shows the the event rate in those referred directly for cardiac testing is significantly higher compared to the background population and to the NSCP group.

Table 5: number of events in the patients referred directly for cardiac testing, the study population and Background population.

	Referred for cardiac testing	Study population	Background population
number(n)	211	229	722
event (n)	11	2	4
%	5.2	0.9	0.6
CI %	2.8-8.9	0.1-2.9	0.2-1.3

Discussion

This is the first study to our knowledge to evaluate the role of non-contrast CT in a NSCP population.

We showed that CAC can be detected in roughly half of patients with NSCP, and the occurrence does not differ significantly from what can be found in the general population. Furthermore, the CAC prevalence and prognosis for NSCP patients does not differ from the prognosis in the asymptomatic background population. However comparing NSCP patients and background population with those referred for cardiac investigation at index contact showed the latter to have a significant higher rate of clinical events. Our study demonstrated that results of non-contrast cardiac CT in NSCP patients does not differ from the general population, and we thus do not consider the results of this examination as a potential stratification tool for NSCP patients compared to use of cardiac CT in the background population. The use of cardiac CT scan for CAC appears to be of limited value in the setting of patients with NSCP, and will in the worst case scenario lead to more downstream test utilization.

Laudon et al. (14) showed that in non-cardiac chest pain patients presenting to the ED and fulfilling the criteria for UAP, the prevalence of CAC was 49%, which is consistent with our findings in NSCP patients. Non-cardiac chest pain patients, all though excluded for MI, compromise a heterogeneous group and also include patients with other causes of chest pain than cardiac related. In Laudon's study non-cardiac chest pain patients with a CAC=0 had a 5 year probability of event free survival of 100%. This was significantly better than the cardiac related chest pain group, implying that a non-contrast CT scan may be useful in the discrimination between non-cardiac related and cardiac related chest pain. However, the study by Laudon et al included patients fulfilling the criteria for unstable angina, who were scanned during index contact, which makes their patient population a higher risk than our patients. NSCP patients in our study were scanned after discharge and exclusion for high risk patients that were referred for further investigation at index contact

The Society of Cardiovascular Computed Tomography Guidelines recommends (15) that patients in the emergency department with acute chest pain, a negative ECG, normal biomarkers and low to intermediate pretest likelihood by risk stratification and in whom a non-coronary cause of the chest pain has been excluded, should be referred for a coronary CT angiography. In the present study we found that patients referred for early further work up, had a one-year event rate of 5 %, as oppose to the approximately 1 % demonstrated in NSCP patients, who from a clinical point of view did not require additional early diagnostic work up. Thus, the current clinical assessment when it comes to risk stratification to distinguish the patients who need further investigations from the NSCP patients seems to be efficient. The differences in

characteristics between those referred for further investigations and those included in our study (without referral at index contact) is however not further elucidated in this study.

It is not possible to conclude on the prognostic value of CAC in predicting adverse cardiac event due to the low number of event in our study, the short follow up time and small number of participants. However the two patients in the NSCP study population experiencing a clinical event had a high CAC score, respectively 349 and 2595, and were known with three risk factors for CVD (hypertension, hypercholesterolemia and a family history of CVD). This may suggest a benefit from combining traditional risk factors with the presence of severe CAC. In concordance with previous studies that found a pooled event rate of 0.3-0.6%/year with CAC=0, the risk of cardiac events is very low when CAC=0 (16). In the NSCP population no events among patients with a CAC=0 was observed, while one person in DanRisk with CAC=0 experienced VT.

The NSCP population compromised more patients with hypercholesterolemia vs DanRisk (43% vs 18%). We know from previous studies that NSCP is associated with more frequent contacts to the health care system and use of medication than the background population (17). This could partially explain that more patients in this group could have been diagnosed with hypercholesterolemia. However, the higher prevalence of CAC in the NSCP population might be explained by more patients having hypercholesterolemia compared to the DanRisk population. The effect of statins on coronary calcification has also demonstrated conflicting results with a previous study showing a trend toward increasing atheroma calcification with statin use (18).

Strengths /Limitations

The outcome data collected from the Danish registries are well documented and validated, which adds strength to this study (19, 20). The patients included in this study are low risk patients. It cannot be excluded that the participating patients included in this study and DanRisk are healthier as it is known that non-participants in clinical trials are at higher risk and have worse outcomes than participants (21). NSCP and Background population were preselected and excluded for known CAD and revascularisation or coronary angiography within the last 5 years, and this excludes the higher risk patients. Conversely, both NSCP and DanRisk participants had to have one risk factor for CAD to fulfill inclusion criteria excluding very low risk patients without risk factors. Patients who at index admission were referred for further investigations were not included in this study. They could have a higher prevalence of CAC which cannot be accounted for in this study.

Age was also a selection criterion in both studies, focusing on 30-70 years old among NSCP patients and 50 and 60 years old in DanRisk. Both studies are most useful in evaluating the middle age patients. However, we do know that increasing age leads to increasing calcification and the use of CAC in an older population is

hence not useful. The low age among both populations in contraire could be a causal explanation for the few events taking place.

The definitions of risk factors were not similar. Family history was limited by age in the DanRisk study while no age limitation existed in NSCP patients, and that could explain the higher proportion of patients with family history of CAD among NSCP patients. The data gathering furthermore differed, as NSCP patients were acutely admitted and values extracted from an acute setting, while DanRisk patients were investigated in a baseline examination. E.g the blood pressures were not obtained uniformly and thus not comparable.

Conclusion

Based on the results of this study the occurrence of CAC patients with NSCP does not differ significantly from what is found in the background population, when adjusted for established risk factors. Thus, a little more than half of the NSCP patients have detectable CAC on a cardiac CT scan. Of notice, the prognosis in these patients is excellent with an overall clinical event rate of less than 1%. The results of the present study indicate that patients at increased risk of future clinical events already are being taken care of during the index hospital contact.

Contributorship

The steering commitee (NI, HM, AL, AD, CBM) designed the trial. NI and CBM obtained funding. The investigators (JL,FH, RA, JB, NPS, MHG) trained the staff and gathered data. NI, AD, MGH and CBM analysed the data. NI, CBM, HM, AL and AD wrote the report. All authors, can take responsibility for the integrity of the data and the accuracy of the data analysis, contributed to the implementation of the study, data interpretation and approved the final report for publication.

Data sharing

No additional data available.

Conflict of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) no authors have support from any company for the submitted work. (2) no authors have relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no

financial relationships that may be relevant to the submitted work; and (4) no authors have non-financial interests that may be relevant to the submitted work.

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Protocol Registration and Results System

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Study Identification

Unique Protocol ID:	SHS-ED-2014-01
Brief Title:	Non-contrast Cardiac CT as a Risk Stratification Tool in Patients With Non-cardiac Chest Pain
Official Title:	
Secondary IDs:	

Study Status

Record Verification:	February 2016
Overall Status:	Completed
Study Start:	September 2014 []
Primary Completion:	June 2015 [Actual]
Study Completion:	June 2015 [Actual]

Sponsor/Collaborators

Sponsor:	University of Southern Denmark
Responsible Party:	Principal Investigator Investigator: Christian Backer Mogensen [cmogensen] Official Title: associate professor Affiliation: University of Southern Denmark
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: S-20140055 Board Name: The Regional Scientific Ethical Committees for Southern Denmark Board Affiliation: Region of Southern Denmark Phone: +45 7663 8221 Email: komite@rsyd.dk Address: Regionshuset

Damhaven 12
7100 Vejle
DENMARK

Data Monitoring: No

Plan to Share IPD:

FDA Regulated Intervention: No

Study Description

Brief Summary: Background:

Only around 20% of all patients seen in hospital with suspected Acute Coronary Syndrome will have Acute Myocardial Infarction. However, several studies indicate that patients where ACS had been excluded by conventional methods sustain a higher cardiac morbidity and mortality than the background population. Not all of these patients can be identified by traditional risk factors such as cholesterol, hypertension, and diabetes or with conventional methods such as ECG, troponin and clinical symptoms. Non-Contrast Cardiac-CT measures the amount of calcification in the coronary arteries and might be a useful addition in predicting future cardiac events in this patient group. The aim of this study is through a double-blinded study to determine whether non-contrast CT scan with calcium score can be used to identify patients at increased risk of death and cardiac event within the following 12 months after an acute admission where troponin measurements were normal.

Methods:

The study will investigate patients with suspected Acute Coronary syndrome who have been examined and subsequently sent home from an emergency- or cardiology department without ACS or another obvious explanation. 750 patients, age 30-70 years who are included in the study: "Identification of risk factors in non-cardiac chest pain patients" will be offered a non-contrast CT scan with calcium score within 14 days after the hospital contact. The participants will be included in a 12 months follow up, where the result of the calcium score is not revealed neither for the patient nor the investigator. After 12 months the results of the scan is compared with the rate of cardiac events. This project is a multicenter study and recruits patients from 6 emergency - and cardiology departments in the region of Southern Denmark.

The study commences at September 2014 and results of this project are expected to contribute to the risk stratification of Non-cardiac chest pain patients.

Detailed Description:

Conditions

Conditions: Coronary Artery Disease

Keywords:

Study Design

Study Type: Observational

Observational Study Model: Cohort

Time Perspective: Prospective

Biospecimen Retention:	None Retained
Biospecimen Description:	
Enrollment:	248 [Actual]
Number of Groups/Cohorts:	1

Groups and Interventions

Intervention Details:
Non-contrast Cardiac CT scan

Outcome Measures

Primary Outcome Measure:

1. major cardiac events
   major cardiac events: cardiac deaths, revascularization, ischaemic related arrythmias, cardiac related readmissions

   [Time Frame: one year]

Eligibility

Study Population:	The study will investigate patients with suspected Acute Coronary syndrome who have been examined and subsequently sent home from an emergency- or cardiology department without ACS or another obvious explanation. 750 patients, age 30-70 years
Sampling Method:	Non-Probability Sample
Minimum Age:	30 Years
Maximum Age:	70 Years
Sex:	All
Gender Based:	
Accepts Healthy Volunteers:	No
Criteria:	Inclusion Criteria: • chest pain with normal cardiac enzymes. • legal competent • age 30-70 years Exclusion Criteria: • chest pain of obvious reason • previous acute coronary syndrome • previous coronary artery investigations within last five years • patients referred for other cardiac examinations after the current admission

Contacts/Locations

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Central Contact Backup:	Christian B Mogensen, M.D. Telephone: +45 79971123

Email: christian.backer.mogensen@rsyd.dk

Study Officials:

Locations: Denmark
Sygehus Soenderjylland
Aabenraa, Denmark, 6200

References

Citations:

Links:

Study Data/Documents:

Table 1 : Participants and non-participants comparison

	Participants		Non-participants		P-value*
	n=229	%	n=212	%	
Characteristics					
Median Age (years/IQR)	57(50-64)		52 (44-60)		0.001
Male	98	43	89	42	0.863
Diabetes mellitus	22	10	10	5	0.048
Hypertension	91	40	70	33	0.143
Hypercholesterolemia	97	42	67	32	0.020
Family history	124	54	93	44	0.031
Smoking	58	25	57	27	0.709

P values compares the proporiotions of participants and non-participants that are known with the specific variable

Table 2: Descriptive characteristisc of NSCP and background population.

	NSCP population		Background population		P-value*
	n=229	%	n=722	%	
					0.476
Female	131	57	327	55	
Male	98	43	295	45	
Age					0.001
30-39	7	3	-		
40-49	46	20	-		
50-59	76	33	316	44	
60-70	100	44	406	56	
Hospital					0.001
Odense	70	31	175	24	
Vejle	63	27	171	24	
Aabenraa	58	25	-	-	
Svendborg	38	17	180	25	
Esbjerg	-	-	196	27	
Hypertension	91	40	266	37	0.458
Hypercholesterolemia	97	42	126	18	0.001
Diabetes	22	10	59	8	0.509
Family history	124	54	287	40	0.001
Smoking	58	25	314	44	0.001
	Mean		Mean		
Systolic blod pressure (mmhg)	144		137		0.001
Diastolic blod pressure (mmHg)	97		83		0.002
Pulse (rate/min)	74		71		0.001
Total cholesterol mmol/L	5.2		5.5		0.005
LDL cholesterol mmol/L	3.1		3.2		0.067
HDL cholesterolmmol/L	1.4		1.5		0.088
BMI (kg/m2)	27		27		0.715

*P values estimates for comparison of mean values.

Table 3: Median CAC estimates based on characteristics variable

	NSCP	Background population	
	Median CAC (IQR) AU	Median CAC (IQR) AU	P-value*
Female	0(0;67)	0(0:18)	0.736
Male	18(0;83)	9(0;116)	0.117
Age			
30-39	0(0;1)		
40-49	0(0;5)		
50-59	0(0;33)	0(0;12.5)	0.247
60-70	47(0;147)	7(0;110)	0.008
Hospital			
Odense	0(0;26)	1(0;69)	0.019
Vejle	8(0;104)	4(0;28)	0.109
Aabenraa	10(0;120)	-	-
Svendborg	16(0;65)	0(0;61)	0.083
Esbjerg	-	0(0;66)	-
Hypertension	30(0;251)	4(0;96)	0.022
Hypercholesterolemia	6(0;94)	14(0;127)	0.878
Diabetes	61(0;253)	11(0;129)	0.251
Familiar history of CVD	3(0;72)	1(0;36)	0.198
Smoking	4(0;133)	5(0;73)	0.607

* P value compares median value of CAC (AU) between NSCP and background population.

Table 4 : The distribution of CAC and endpoints for NSCP and background population.

	Total		CAC=0 AU		CAC>0 AU	
	n	%(CI)	n	%(CI)	n	%(CI)
NSCP	2/229	0.9(0.2-2.9)	0/106	0(0.0-3.0)	2/123	1.6(0.3-5.3)
Background population	4/722	0.6(0.2-1.3)	1/350	0.3(0.1-1.4)	3/372	0.8(0.2-2.2)

Table 5: number of events in the patients referred directly for cardiac testing, the study population and Background population.

	Referred for cardiac testing	Study population	Background population
number(n)	211	229	722
event (n)	11	2	4
%	5.2	0.9	0.6
CI %	2.8-8.9	0.1-2.9	0.2-1.3

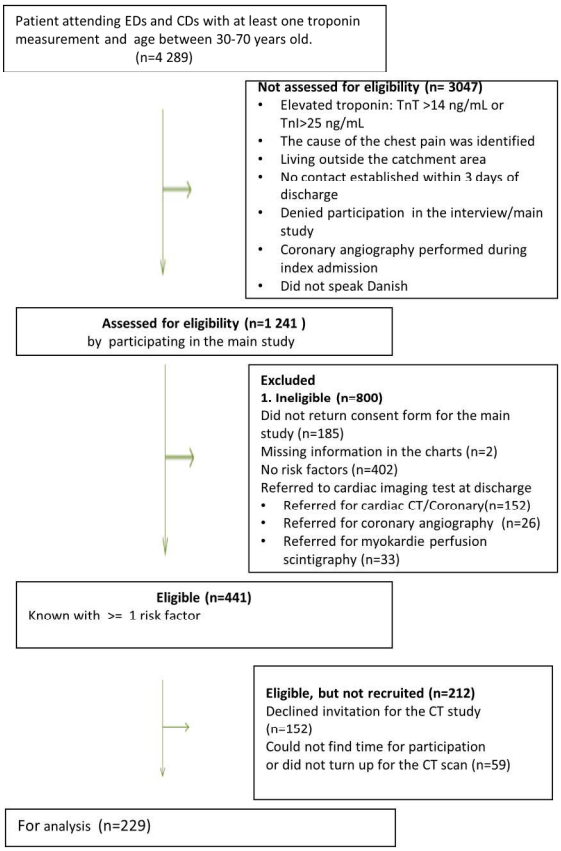

Figure 1: Flowchart for the inclusion of the NSCP population

254x338mm (300 x 300 DPI)

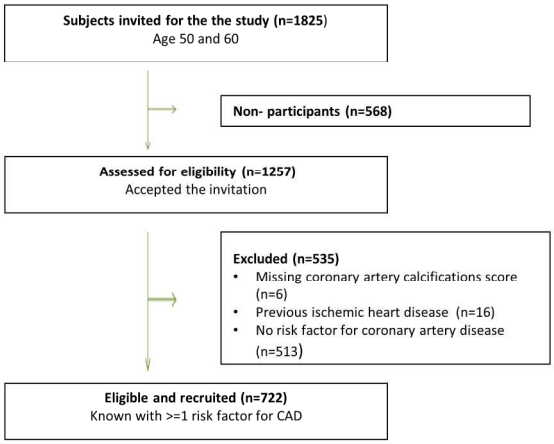

Figure 2: Flow chart for DanRisk

254x338mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (Page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page 1)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page 2)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page 3)
Methods		
Study design	4	Present key elements of study design early in the paper (Page 3)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page 3-6)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Page 3-4) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page 4)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Page 4-5)
Bias	9	Describe any efforts to address potential sources of bias (Page 6)
Study size	10	Explain how the study size was arrived at (Page 6)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Page 6)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Page 7)
		(*b*) Describe any methods used to examine subgroups and interactions (Page 6-7)
		(*c*) Explain how missing data were addressed (Page 4)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Page 7)
		(b) Give reasons for non-participation at each stage (Page 9)
		(c) Consider use of a flow diagram (Page 9)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Page 10)
		(b) Indicate number of participants with missing data for each variable of interest (None, missing CAC not included in the study)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (Page 12)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (Page 12-13)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Page 12)
		(*b*) Report category boundaries when continuous variables were categorized (Page 12)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Page 13)
Discussion		
Key results	18	Summarise key results with reference to study objectives (Page 14)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Page 15)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page 14-15)
Generalisability	21	Discuss the generalisability (external validity) of the study results (Page 16)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (Page 17)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The Prevalence of Coronary Artery Calcium in a on-specific Chest Pain Population in Emergency and Cardiology Departments compared to the Background Population – a prospective cohort study with 12 months follow up for clinical endpoints

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The Prevalence of Coronary Artery Calcium in a on-specific Chest Pain Population in Emergency and Cardiology Departments compared to the Background Population

– a prospective cohort study with 12 months follow up for clinical endpoints.

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Abstract

Objectives: To examine the prevalence of Coronary Artery Calcification (CAC) and frequency of cardiac events in a cohort of Non-Specific Chest Pain (NSCP) patients (an acute admission for chest pain and discharged without an obvious reason for the chest pain) and compare with the background population.

Design: A double blinded prospective observational cohort study examined with measurement of the CAC score and one year of follow-up.

Setting: Departments of Emergency Medicine and Cardiology in the Southern Region of Denmark.

Subjects: 229 NSCP patients were compared with 722 subjects from the background population.

Main outcomes measures: Prevalence of CAC, incidence of unstable angina (UAP), acute myocardial infarction (MI) , ventricular tachycardia (VT), coronary revascularization and cardiac related mortality.

Results: No significant difference in prevalence of CAC (Odds ratio (OR) 0.9 (95%CI: 0.6-1.3), p=0.546) or frequencies of endpoints (p=0.64) were found. The OR for CAC >100 AU was 1.0 (95% CI:0.6-1.5) p=0.826 for NSCP patients compared to the background population. During one year follow-up two (0.9%) NSCP

patients were revascularised, while none experienced UAP, MI, VT or death. In the background population four (0.6%) had a clinical endpoint; two MI, one VT and one cardiac related death.

Conclusion: The prevalence of CAC (CAC>0 AU) among NSCP patients was comparable with the background population. The risk of an event was low. A CAC examination seems not to be useful in the case of NSCP patients.

Strength and limitations

- The patients were unselected and all-comers.
- The patients were included from six hospitals.
- The number of included patients was relatively small.
- No patients were lost to follow-up.
- Few events occurred during follow-up.

Introduction

Cardiovascular disease (CVD) remains a major public health problem and is the number one cause of death among men and women in Europe and United State (1-3). Less than one in five patients with chest pain in the emergency departments turns out to fulfill the diagnostic criteria of acute myocardial infarction (MI) (4, 5). Other causes of acute chest pain may be of cardiovascular origin (aneurism, aortic dissection pulmonary embolism), but can also be non-cardiac related (gastrointestinal disorders, musculoskeletal disorders) while in a significant number of patients the cause of symptoms remains unknown, and these patients are defined as having Non-Specific Chest Pain (NSCP) (6).

However, even if acute MI is definitely excluded, coronary artery disease (CAD) may be present with an inherent risk of future cardiac events. Hence, 0.8% -2.1% of the patients excluded for MI experienced an adverse outcome during 30 days follows up after discharge from an emergency department (7, 8). It has been shown that up to 20% of patients with CAD do not have any traditional risk factors such as hypertension, hyperlipidemia, diabetes or smoking (9), thus a non-contrast cardiac CT might serve as a tool in risk stratification by measuring the presence and extent of coronary artery calcium (CAC). The advantages of non-contrast cardiac CT are that the method is easy to perform and interpret, the reproducibility is high and the radiation exposure is low (10-13). The role of a non-contrast cardiac CT as a risk stratification tool has been established in asymptomatic persons (14, 15) . The prevalence of CAC in an asymptomatic general population without known prior CVD has been shown to be 44%-50% (16, 17). However, the clinical importance of CAC in patients with acute chest pain, in whom an acute MI has been ruled out, remains to be investigated.

In order to evaluate the non-contrast cardiac CT as a potential risk stratification tool for patients with NSCP the aim of the present study was twofold. First, we wanted to investigate the prevalence of CAC among NSCP patients and to compare the findings with observations from an asymptomatic background population. Second, we wished to examine the frequency of clinical cardiac events related to CAC in NSCP patients during a 12 months follow-up period, and compare these data with the results from the

asymptomatic background population but also the NSCP patients who were directly referred for a further cardiac test from index contact.

Method and materials

Study design

This study was a double blinded prospective observational cohort study that included patients from the emergency and cardiology departments in the Region of Southern Denmark. All patients with an acute visit for chest pain and suspicion of cardiac ischemia admitted to the hospitals in Odense, Svendborg, Vejle, Kolding, Aabenraa or Sonderborg, and at least one troponin measurement during the contact were included. Chest x-ray, CT scans, echocardiography and other diagnostic tests during the admission were applied at the sole discretion of the attending physician, but not used in this study. The inclusion period was from September 2014 until May 2015. The patients were invited for this study, if they were discharged with a NSCP diagnosis (ICD codes: DR072/DR073/DR034/DR035) and without any obvious reason for the chest pain. Furthermore we excluded patients who were referred directly for further cardiac imaging test by the discharging physician.

Study population

Through the central biochemical laboratory for all hospitals in the region of Southern Denmark, all patients with measurement of troponin in the emergency and cardiology departments were identified on a daily basis. Electronic patient files were scrutinized in all patients with normal troponin values, as defined below. Patients had to complete a structured questionnaire by a telephone interview within three days of discharge from the index admission.

Afterwards written information and a consent form for participation was sent to the patient. Patients who returned the consent form were scheduled for the CT scan. The participant and the physicians were blinded for the result of the non-contrast CT.

The inclusion and exclusion criteria for the study is defined below

Inclusion criteria:

- Normal troponin (high sensitivity troponin T <14 ng/L or high sensitivity troponin I< 25 ng/L)
- Age 30-70 years
- Known with one risk factor for CAD (present smoker, hypertension, hypercholesterolemia, familiar disposition to CVD, and diabetes mellitus).

Exclusions criteria:

- Living outside the catchment area of Region of Southern Denmark
- Refusing participation in the telephone interview and or CT scan
- Previous history of CAD defined as MI or coronary revascularization.
- Coronary angiography/cardiac CT or myocardial scintigraphy performed within the last 5 years.
- None Danish speakers

We used the Danish Risk Score study (DanRisk) population (17) as a control group representing the background population. The DanRisk study population consisted of 1 257 asymptomatic subjects aged 50 and 60 years old, who in 2009 had been examined in one of four cardiac computer tomography (CT) centers (Odense, Esbjerg, Vejle or Svendborg) in the Region of Southern Denmark. The exclusion criteria in the present study are asymptomatic individuals without risk factors for CAD (hypertension, hypercholesterolemia, familiar disposition, known smoker and diabetes mellitus), known CAD and missing CAC scores.

Definitions

In the NSCP population comorbidity was self-reported. Diabetes mellitus was defined as the use of antidiabetic medication or a diagnosis given by their general practitioner. Hypertension and hypercholesterolemia were present if the patients stated to be in relevant medical treatment or had received the diagnoses by the general practitioner. Family history was defined as a first degree relative with CVD without consideration to age. Smoking was defined as a current smoker. Systolic and diastolic blood pressure and heart rate were retrieved from the patient files, as the first measured value during the index admission. Cholesterol values were collected up to three months before and three months after the index admission. The value closest to the index date was used. BMI was calculated based on self-reported height and weight.

For the background population diabetes mellitus was defined as use of anti-diabetic medication that included any oral antidiabetic drug and/or insulin. Hypertension was defined as the use of antihypertensive medical treatment. Hypercholesterolemia was defined as use of lipid lowering medication. Family history was defined as first degree relative with CVD, male <55 years and female <65 years. Smoking was defined as current smoker. Blood pressure, heart rate, BMI and cholesterol values were measured at baseline examination.

Troponins

The cardiac troponin I, used by Odense University Hospital, was analyzed by use of the Abbot Diagnostics architect with an upper reference limit of 99th percentile of 25 ng/L and a coefficient of variation < 10% at 5 ng/L. The decision limit for MI was set at ≥ 25 ng/L

Troponin T, used by all other participating hospitals, was analysed by Roche diagnostic elecsys 2010, modular analytics E170, Cobas e411, cobas e601. The 99th percentile upper reference limit was 14 ng/L and a coefficient variation <10% at 13 ng/L. The decision limit was set ≥ 14 ng/L for MI.

Cardiac CT protocol

CAC was assessed by summing the scores from all foci in the coronary arteries and expressed in Agatston unit (AU) (10). CAC was assessed by trained radiographers, and reanalysed by the first author in 52 subjects. Two centers used dual-source CT scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany) with prospective ECG triggering. In persons with heart rate <75 beats/minute the ECG triggering was set in diastolic phase at 65-75% of the cardiac R-R interval. In persons with heart rate ≥75 beats/min the ECG triggering was set in systolic phase at 250-400 ms. Additional settings: sequential prospective scan, slice thickness 3 mm, collimation 128 x 0.6 mm, gantry rotation time 0.28ms, 120 kV tube voltage, 90 mAs/rotation.

One center used a GE 64-slice CT-scanner (Discovery 750 HD; GE Healthcare). In persons with heart rate <75 beats/minute the ECG triggering was set in diastolic phase at 75% of the cardiac R-R interval. In persons with heartrate ≥75 beats/min the ECG triggering was set in systolic phase at 40% of the cardiac R-R interval. Additional settings: sequential prospective scan, slice thickness 2.5 mm, collimation 64 x 0.625 mm, gantry rotation time 0.35ms, 120 kV tube voltage and 200 mA tube current.

The last center used a Toshiba Aquillion ONE Next Generation (Toshiba Medical systems) CT scanner with prospective ECG triggering. If heart rate was <75 bpm the ECG triggering was in the diastole phase at 65%-75% of the R-R interval. In persons with heart rates ≥75 beats/min the ECG triggering was set in systolic phase at 40%. Additional settings: sequential prospective scan, slice Thickness was 0.5 mm, collimation after scan range 0.5 mm x 240 – 320, gantry rotation time 0.275 ms and 120 kV tube voltage.

Follow-up

The study was conducted as a double blinded study with a 12 month follow-up time. Neither the participants nor the investigators knew the results of the CAC score before the end of follow-up. By then the participants and their general practitioner received a letter with the results of the CAC score.

The clinical endpoints in the follow-up study were unstable angina (UAP), non-fatal MI, ventricular tachycardia (VT), coronary revascularization and cardiac death. The endpoints were compared with the background population. Furthermore we did a comparison with NSCP patients who were referred for cardiac imaging testing at the index admission and thus did not participate in our study. These patients were referred for further diagnostic testing by the physician on call that evaluated these patients to have a higher risk of CAD.

Sample size

A sample size calculation was performed before the study. The prevalence of elevated CAC score (CAC>0 AU) in the Dan Risk background asymptomatic population was 44%. We assumed that the prevalence of CAC score in our symptomatic low risk population was at least 18% point higher, i.e. 62%, since on a symptomatic population referred for coronary angiography 79% had a CAC>0 AU (13). In order to detect a risk factor with a size of at least OR 2.1 in the group exposed to the factor, with a significance level of 95% and a power of 80% and a ratio 1 of exposed/non-exposed we needed a sample size of at least 238 patients, using Fleiss method.

Statistical analyses

Categorical variables are presented with frequency tables and percentages. Distributions of all continuous variables were evaluated by empirical histograms, and normally distributed variables are presented as mean and standard deviation (SD), while skewed distributed continuous variables are presented as median and interquartile range (IQR). Fischer's exact test and Chi square test are used for categorical variables, t-test for comparison of normally distributed variables, while the Wilcoxon's rank sum test are used skewed distributed variables. In multivariate analyses including the traditionally risk factors (gender, age, smoking, hypertension, hypercholesterolemia, diabetes mellitus, body mass index and family history of cardiovascular disease) the prevalence of CAC (the outcome variable) >0 and CAC >=100 among the NSCP patients and background population were compared. Pearson's correlation was used to measure the agreement between two CAC score readers in 52 cases. The correlation coefficient was 99%. Analyses were performed with STATA SE 14 (StataCorp, College Station, TX, USA). A two-sided P-value < 0.05 was considered statistically significant.

Ethics

The protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20140055) and conducted in accordance with the Declaration of Helsinki. The study was registered in

Clinical trial with number NCT02422316. The study was registered with The Danish Data Protection Agency (2008-58-0035 no 1092). Written informed consent was obtained from each participant.

The DanRisk protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20080140) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Results

In total 4 289 patients aged 30 to 70 years old attended an Emergency or Cardiology Department and had at least one a troponin measurement done. After exclusion of 3 047 patients (i.e. elevated troponin, identified cause of the chest pain, no consent, see Figure 1), 1 241 were left for study eligibility. However, further 800 of these for different reasons (i.e. no risk factors, referred for coronary imaging) had to be excluded from participation in a cardiac CT scan examination. Of the remaining 441 patients with NSCP 229 patients (participants) accepted the invitation, and to underwent a cardiac CT scan, while 212 patients (non-participants) either declined the invitation or did not show up at the time of cardiac CT-scan. The non-participants represented individuals that were eligible but not recruited. The mean age was 57 (IQR 50;64) and 52 (IQR 44;60) years in participants and in non-participants, respectively, p=0.001. Significantly more were known with hypercholesterolemia and a family history of CVD among participants compared to non-participants, while no significant differences were found in gender, diabetes, hypertension or smoking status (Table 1).

Table 1 : Baseline characteristics of participants and non-participants

	Participants n=229(%)	Non-participants n=212	P-value
Age (years)	57(56-58)	52 (50-53)	0.001
Male	98 (43)	89 (42)	0.86
Diabetes mellitus	22 (10)	10 (5)	0.048
Hypertension	91 (40)	70 (33)	0.14
Hypercholesterolemia	97 (42)	67 (32)	0.02
Family history	124 (54)	93 (44)	0.03
Smoking	58 (25)	57 (27)	0.71

Values are n (%) or mean ± SD.

Figure 2 shows the selection of the background population. 1 825 random individuals 50 or 60 years old were invited for participation, and 1 257 accepted the invitation. In the present study a total of 535 individuals were excluded; 513 did not fulfill the criteria of having at least one risk factor, 16 patients were

known with CAD and 6 did not have a CAC score performed. In total, 722 individuals from the DanRisk study served as background population.

Table 2 lists the baseline characteristics for the NSCP patients and the background population. Mean age for the NSCP population was 57 years and 55 years for background population (p=0.007). A significantly higher proportion of NSCP patients had known hypercholesterolemia and a family history of cardiovascular disease, while more from the background population were smokers. Furthermore, a significant difference between the populations regarding blood pressure, heart rate and total cholesterol was found.

Table 2: Descriptive characteristics of non-Specific Chest Pain patients and the background population.

	NSCP patients n=229 (%)	Background population n=722 (%)	P-value
Male	98 (43)	295 (45)	0.48
Age	57 ±9	55 ±5	0.008
30-39	7 (3)	-	
40-49	46 (20)	-	0.001
50-59	76 (33)	316 (44)	
60-70	100 (44)	406 (56)	
Hypertension	91 (40)	266 (37)	0.460
Hypercholesterolemia	97 (42)	126 (18)	0.001
Diabetes	22 (10)	59 (8)	0.51
Family history of cardiovascular disease	124 (54)	287 (40)	0.001
Smoking	58(25)	314(44)	0.001
Previous smoker	74(32)	197(27)	0.142
Non-smoker	97(42)	211(29)	0.001
Systolic blood pressure (mmHg)	144 ±30	137 ±19	0.001
Diastolic blood pressure (mmHg)	97 ±122	83 ±10	0.002
Heart rate	74 ±14	71 ±14	0.001
Total cholesterol (mmol/L)	5.2 ±1.1	5.5 ±1.1	0.005
LDL cholesterol (mmol/L)	3.1 ±0.9	3.2 ±0.9	0.070
HDL cholesterol (mmol/L)	1.4 ±0.5	1.5 ±0.5	0.080
BMI (kg/m^2)	27 ±6	27 ±5	0.715
CAC score (AU)	2(0:74)	1 (0:54)	0.230
0	106 (46)	350 (48)	0.679
1-99	74(32)	238(33)	0.897
≥ 100	49(22)	134(19)	0.438

Values are n (%), mean ± SD, or median (IQR). NSCP = non-Specific Chest Pain, AU=Agatston unit

The prevalence of the CAC score categories (0 AU, 1-99 AU ≥100 AU) were similar (46%, 32%, 22% versus 48%, 33% and 19%, p=0.630) for NSCP and background population, and there was no difference in the

median CAC score (2 AU (IQR 0;74 AU) and 1 AU (IQR 0;54 AU), p=0.229). In the subgroups there was no difference in the median CAC scores between NSCP patients and the background population concerning females (0 AU (IQR 0;67 AU) and 0 AU (IQR 0;18 AU), p=0.74), males (18 AU (IQR 0;83 AU) and 9 AU (IQR 0;116 AU), p=0.12), and the 50-59 years old (0 AU (IQR 0;33 AU) and 0 AU (IQR 0;12.5 AU), p=0.25), while the 60-69 years old had a higher median CAC score (47 AU (IQR 0;147 AU) versus 7 AU (IQR 0;110 AU), p=0.008). In the multivariate logistic regression analysis no significant difference was found between the presences of CAC in the NSCP vs the background population (Odds ratio (OR) 0.9 (95%CI: 0.6-1.3), p=0.546). The OR for CAC >100 AU was 1.0 (95% CI:0.6-1.5) p=0.826.

In 52 cases two independent readers performed the CAC score measurement, and Pearson's correlation was 99%.

During one year of follow-up 2 out of 229 NSCP patients were revascularized, while no one had UAP, MI, VT or died from cardiac related causes. The two patients with events were a female aged 64 and a male aged 60 years with a CAC score of 349 and 2 595, respectively. Both were known with hypertension, hypercholesterolemia and a family history of CVD. The event rate in the background population was 4 out of 722; two had MI, one had VT and one cardiac related death. All four patients were males. The patient with VT was 50 years, and had a CAC=0, but also a family history of CVD. The three remaining were 60 years old with a CAC score of 166, 832 and 1326 respectively. One was a smoker, one had hypertension and hypercholesterolemia, while the last was smoking, had diabetes and a family history of CVD. Fishers exact test showed no statistically difference in the incidence of endpoints between NSCP and background population (0.9% (95%CI: 0.1-2.9) vs 0.6% (95%CI: 0.2-1.3), p=0.64).

211 patients were referred for further work up from the index contact and not included in this study. 152 went through a cardiac CT, 26 were referred for coronary angiography and 33 for myocardial perfusion scintigraphy. Two patients had UAP, two had MI and nine had coronary revascularization performed during one year of follow-up. No one had VT or died from cardiac related causes. 11 out of 211 patients (5.2% (95%CI: 2.8-8.9)) had an event, and the rate was significantly higher in this group of patients compared to the NSCP patients and background population (p=0.001).

Discussion

This is the first study to our knowledge to evaluate the role of non-contrast CT in a NSCP population.

We showed that CAC can be detected in roughly half of patients with NSCP, and the occurrence does not differ significantly from what can be found in the general population. Furthermore, the prognosis for NSCP

patients does not differ from the prognosis in the asymptomatic background population. However comparing NSCP patients and background population with those referred for cardiac investigation at index contact showed the latter to have a significant higher rate of clinical events. As the CAC score in NSCP patients does not differ from the general population, we thus do not consider the results of a non-contrast CT scanning as a potential stratification tool for NSCP patients. The use of cardiac CT scan for CAC appears to be of limited value in the setting of patients with NSCP, and could in the worst case scenario lead to more downstream test utilization.

Laudon et al. (18) showed that in non-cardiac chest pain patients presenting to the ED and fulfilling the criteria for UAP, the prevalence of CAC was 49%, which is consistent with our findings in NSCP patients. Non-cardiac chest pain patients, all though excluded for MI, compromise a heterogeneous group and also include patients with other causes of chest pain than cardiac related. In Laudon's study non-cardiac chest pain patients with a CAC=0 had a 5 year probability of event free survival of 100%. This was significantly better than the cardiac related chest pain group, which implies that a non-contrast CT scan may be useful in the discrimination between non-cardiac related and cardiac related chest pain. However, the study by Laudon et al included patients fulfilling the criteria for unstable angina, who were scanned during index contact, which makes their patient population a higher risk than our patients. NSCP patients in our study were scanned after discharge and exclusion for high risk patients that were referred for further investigation at index contact.

The Society of Cardiovascular Computed Tomography Guidelines recommends (19) that patients in the emergency department with acute chest pain, a negative ECG, normal biomarkers and low to intermediate pretest likelihood by risk stratification and in whom a non-coronary cause of the chest pain has been excluded, should be referred for a coronary CT angiography. In the present study we found that patients referred for early further work up, had a one-year event rate of 5 %, as opposed to the approximately 1 % demonstrated in NSCP patients, who from a clinical point of view did not require additional early diagnostic work up. Thus, the current clinical assessment when it comes to risk stratification to distinguish the patients who need further investigations from the NSCP patients seems to be efficient. The differences in characteristics between those referred for further investigations and those included in our study (without referral at index contact) are however not further elucidated in this study.

It is not possible to conclude on the prognostic value of CAC in predicting adverse cardiac event due to the low number of event in our study, the short follow up time and small number of participants. However the two patients in the NSCP study population experiencing a clinical event had a very high CAC score, respectively 349 and 2595, and were known with three risk factors for CVD (hypertension, hypercholesterolemia and a family history of CVD). This is in agreement with numerous previous studies

showing that high CAC score is major and independent risk factor (20). In concordance with previous studies we found a very low event rate in patients without CAC (21). In the NSCP population no events among patients with a CAC=0 was observed, while one person in background population with CAC=0 experienced VT.

The NSCP population compromised more patients with hypercholesterolemia vs background population (43% vs 18%). We know from previous studies that NSCP is associated with more frequent contacts to the health care system and use of medication than the background population (22). This could partially explain that more patients in this group could have been diagnosed with hypercholesterolemia.

Strengths /Limitations

The outcome data collected from the Danish registries are well documented and validated, which adds strength to this study (23, 24). The participating patients included in this study and background population might be healthier than the non-participants as in clinical trials the latter are at higher risk and have worse outcomes than participants (25). The NSCP patients and the background population were preselected as we excluded individuals without risk factors and patients with known CAD and coronary angiography within the last 5 years. Thereby the results are not applicable to very low risk and high risk patients. We know from previous validation studies that the self-reported data for CVD is under reported and inaccurate compared to measured data (26, 27). A sensitivity of 84.5% has been shown for hypertension, hypercholesterolemia and diabetes (26). This could have influence the selection of our patients, since presence of risk factors were one of our inclusion criteria. Patients who at index admission were referred for further investigations were not included in this study. They could have a higher prevalence of CAC which cannot be accounted for in this study.

The definitions of risk factors were not similar. Family history was limited by age in the DanRisk study while no age limitation existed in NSCP patients, and that could explain the higher proportion of patients with family history of CAD among NSCP patients. The data gathering furthermore differed, as NSCP patients were acutely admitted and values extracted from an acute setting, while DanRisk patients were investigated in a baseline examination. E.g. the blood pressures were not obtained uniformly and thus not comparable.

The different scanners and protocols used might have had an effect on the presence of CAC. However, the centers and scanners used for the CAC assessment in the NSCP patients and background population were almost the same and comparable for that reason.

Finally, the study is underpowered to show any differences in events. Thus, the study is an observational study on the prevalence of CAC in NSCP patients.

Conclusion

Based on the results of this study the presence of CAC in NSCP patients does not differ significantly from what is found in the background population, when adjusted for traditionally risk factors. Thus, a little more than half of the NSCP patients have detectable CAC on a cardiac CT scan. The prognosis in NSCP patients seems to be as good as in the background population with a combined event rate of less than 1%.

Contributorship

The steering commitee (NI, HM, AL, AD, CBM) designed the trial. NI and CBM obtained funding. The investigators (JL, FH, RA, JB, NPS, MHG) trained the staff and gathered data. NI, AD, MHG and CBM analysed the data. NI, CBM, HM, AL and AD wrote the report. All authors, can take responsibility for the integrity of the data and the accuracy of the data analysis, contributed to the implementation of the study, data interpretation and approved the final report for publication.

Data sharing

No additional data available.

Conflict of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) no authors have support from any company for the submitted work. (2) no authors have relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) no authors have non-financial interests that may be relevant to the submitted work.

Figure legends

Figure 1: Flowchart fir the inclusion of NSCP patients

Figure 2: Flowchart for inclusion of the background population

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Figure 2: Flow chart for the background population represented by the DanRisk study patients.

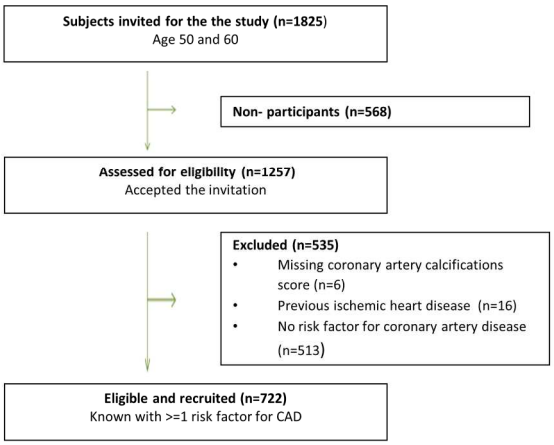

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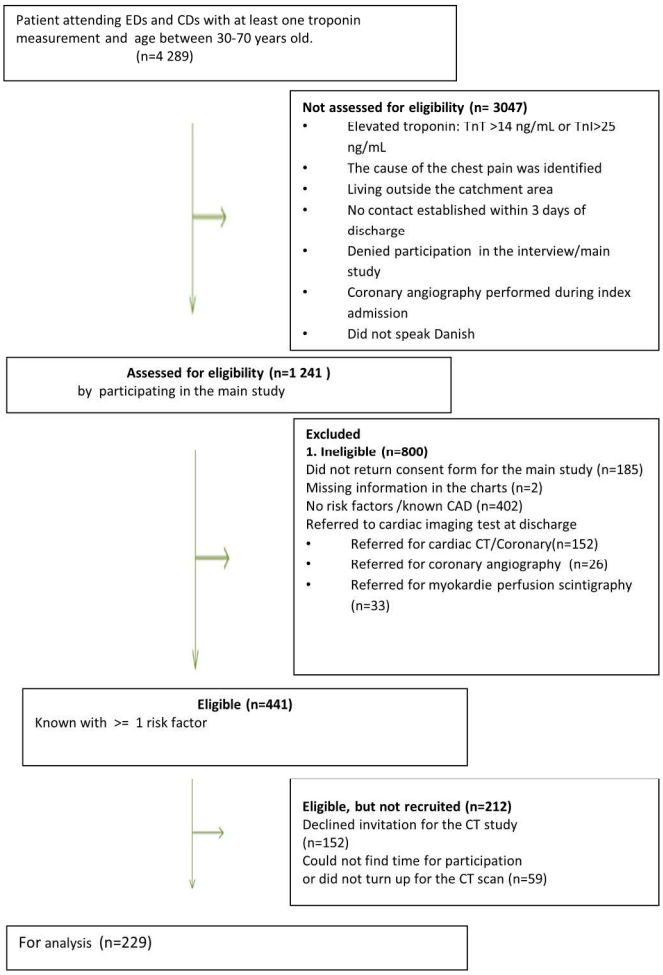
Figure 1: Flowchart for the inclusion of the NSCP population



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (Page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page 1)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page 2)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page 3)
Methods		
Study design	4	Present key elements of study design early in the paper (Page 3)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page 3-6)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Page 3-4) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page 4)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Page 4-5)
Bias	9	Describe any efforts to address potential sources of bias (Page 6)
Study size	10	Explain how the study size was arrived at (Page 6)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Page 6)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Page 7)
		(*b*) Describe any methods used to examine subgroups and interactions (Page 6-7)
		(*c*) Explain how missing data were addressed (Page 4)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Page 7)
		(b) Give reasons for non-participation at each stage (Page 9)
		(c) Consider use of a flow diagram (Page 9)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Page 10)
		(b) Indicate number of participants with missing data for each variable of interest (None, missing CAC not included in the study)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (Page 12)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (Page 12-13)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Page 12)
		(*b*) Report category boundaries when continuous variables were categorized (Page 12)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Page 13)
Discussion		
Key results	18	Summarise key results with reference to study objectives (Page 14)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Page 15)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page 14-15)
Generalisability	21	Discuss the generalisability (external validity) of the study results (Page 16)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (Page 17)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The Prevalence of Coronary Artery Calcification in a Non-Specific Chest Pain Population in Emergency and Cardiology Departments compared to the Background Population – a Prospective Cohort Study in Southern Denmark with 12-month Follow-up of Cardiac Endpoints.

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The Prevalence of Coronary Artery Calcification in a Non-Specific Chest Pain Population in Emergency and Cardiology Departments compared to the Background Population

– a Prospective Cohort Study in Southern Denmark with 12-month Follow-up of Cardiac Endpoints.

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Abstract

Objectives: To examine and compare the prevalence of Coronary Artery Calcification (CAC) and the frequency of cardiac events in a background population and a cohort of Non-Specific Chest Pain (NSCP) patients who present to an emergency or cardiology department and are discharged without an obvious reason for their symptom.

Design: A double-blinded, prospective, observational cohort study that measures both CT-determined CAC scores and cardiac events after one year of follow-up.

Setting: Emergency and cardiology departments in the Region of Southern Denmark.

Subjects: In total, 229 NSCP patients were compared with 722 patients from a background comparator population.

Main outcomes measures: Prevalence of CAC and incidence of unstable angina (UAP), acute myocardial infarction (MI), ventricular tachycardia (VT), coronary revascularization, and cardiac-related mortality one year after index contact.

Results: There was no significant difference in the prevalence of CAC [odds ratio (OR) 0.9 (95% CI: 0.6-1.3), p=0.546] or the frequency of cardiac endpoints (p=0.64) between the studied groups. When compared with the background population, the OR for NSCP patients for a CAC > 100 AU was 1.0 (95% CI:0.6-1.5), p=0.826. During one year of follow-up, two (0.9%) NSCP patients underwent cardiac revascularization, while none experienced UAP, MI, VT, or death. In the background population, four (0.6%) participants experienced a clinical cardiac endpoint; two had an MI, one had VT, and one had a cardiac-related death.

Conclusion: The prevalence of CAC (CAC > 0 AU) among NSCP patients is comparable to a background population and there is a low risk of a cardiac event in the first year after discharge. A CAC study does not provide notable clinical utility for risk stratifying NSCP patients.

Strength and limitations

- The patients were unselected.
- The patients were included from six hospitals.
- The number of participants was relatively small.
- No patients were lost to follow-up.
- Few events occurred during follow-up.

Introduction

Cardiovascular disease (CVD) is a major public health problem and the most common cause of death among men and women in Europe and the United State (1-3). Less than one in five patients presenting to the emergency department with chest pain have acute myocardial infarction (MI) (4, 5). Other potential causes for their symptoms include non-ischemic cardiac disease (aneurysm, aortic dissection, or pulmonary embolism) and non-cardiac disease (respiratory, gastrointestinal, or musculoskeletal disorders). However, for a significant number of patients the cause of symptoms is unclear; such patients are defined as having Non-Specific Chest Pain (NSCP) (6). For these patients, the exclusion of acute MI in an acute care setting does not rule out underlying coronary artery disease (CAD) or the associated risk of future cardiac events, as demonstrated by studies showing that 0.8%-2.1% of patients evaluated for MI and discharged from emergency departments have an adverse cardiac outcome in the first 30 days after discharge (7, 8).

Up to 20% of patients with CAD do not have the traditional CVD risk factors of hypertension, hyperlipidemia, diabetes, or smoking (9). Consequently, there is a need to identify diagnostic tools that can be used to risk stratify patients with chest pain, particularly in an acute care setting. A non-contrast cardiac

CT can be used to measure the presence and extent of coronary artery calcium (CAC) and might serve as one such tool. As a diagnostic test, it offers the advantages of easy performance, simple interpretation, and high reproducibility, while exposing patients to relatively low levels of radiation (10-13). While it has been evaluated as a risk stratification tool in asymptomatic individuals – and demonstrated a CAC prevalence of 44%-50% (14, 15) – its role in patients with NSCP remains uninvestigated.

In order to evaluate the role of non-contrast cardiac CT as a risk stratification tool for patients with NSCP, this study had two goals. The first was to identify the prevalence of CAC among NSCP patients discharged from emergency and cardiology departments, and compare these findings with observations from an asymptomatic background population. The second was to examine the frequency of clinical cardiac events in NSCP patients during a 12-month follow-up period, and compare that data with results from an asymptomatic background population and from a population of higher-risk NSCP patients who are referred for further cardiac testing after index contact.

Method and materials

Study design

The study was a double-blinded, prospective, observational cohort study. It included patients from emergency and cardiology departments in the Region of Southern Denmark, specifically in the cities of Odense, Svendborg, Vejle, Kolding, Aabenraa, and Sonderborg. Patients were enrolled between September 2014 and May 2015 provided they met the following inclusion criteria: they presented to hospital with acute chest pain and a suspicion of cardiac ischemia; they were admitted to hospital; they had at least one troponin measurement; they were discharged with a diagnosis of observation for myocardial infarction or chest pain (ICD10 codes: DR072/DR073/DR034/DR035); and there was no identifiable cause for their chest pain. An additional inclusion criteria was the presence of at least one known risk factor for CAD (current smoker, hypertension, hypercholesterolemia, diabetes mellitus, or significant family history of CVD).

Patients were excluded from the study if they were referred for out-patient cardiac imaging test after the index visit, lived outside the catchment area (Region of Southern Denmark), were unable to speak Danish, declined to either complete a telephone interview and/or undergo a CT scan, or had a previous history of CAD as defined by previous MI or coronary revascularization (Figure 1).

Study population

The study population was identified by performing a daily search of troponin values in the central biochemical laboratory, which stores results for the region of Southern Denmark. Electronic patient files for any emergency or cardiology department patients between the ages of 30-70 were reviewed, and patients with normal troponin values, as defined by a high sensitivity troponin T <=14 ng/L or a high sensitivity troponin I < 25 ng/L, were assessed for study eligibility. Provided they met eligibility criteria they completed a structured telephone questionnaire within three days of discharge from index contact. Thereafter, consent forms and study information were sent out. Those patients who returned the consent form were scheduled for a non-contrast CT scan, the results of which were blinded to participants and investigators until the conclusion of the study.

For comparison purposes, we used the Danish Risk Score study (DanRisk) population (15) as a background comparator group. The DanRisk study population included 1,257 asymptomatic subjects, age 50-60 years, who were examined in one of four cardiac computer tomography (CT) centers in the Region of Southern Denmark (Odense, Esbjerg, Vejle, or Svendborg). From this study population, we excluded asymptomatic individuals without risk factors for CAD (hypertension, hypercholesterolemia, familiar disposition, known smoker and diabetes mellitus), individuals with known CAD, and those missing CAC scores. The remaining group of individuals comprised the comparator group.

Definitions

Comorbidity in the NSCP population was self-reported. Individuals were considered to have diabetes mellitus if they used an anti-diabetic medication or had been given a diagnosis of diabetes mellitus by their general practitioner. Similarly, hypertension and hypercholesterolemia were considered present if participants used medications to treat either disease or if they had received a diagnosis of either illness. Family history was defined as a first degree relative with CVD regardless of age of onset, while smoking was defined by current smoking status. The first blood pressure and heart rate values taken during the index admission were retrieved from patient files. Cholesterol values were collected up to three months before and three months after the index admission, with the value closest to the index date selected for the study. BMI was calculated based on self-reported height and weight.

In the background comparator group, individuals were considered to have diabetes mellitus, hypertension, or hypercholesterolemia if they used an anti-diabetic, hypertension, or cholesterol-lowering medication, respectively. Family history was defined by the presence of CVD in a male first degree relative < 55 years or a female first degree relative < 65 years. Smoking was based on smoking status at the time the study was

conducted. Blood pressure, heart rate, BMI, and cholesterol values were measured during baseline examination.

Troponins

Troponin I, used by Odense University Hospital, was analysed using the Abbot Diagnostics Architect with an upper reference limit of 99th percentile for 24 ng/L and a coefficient variation < 10% at 5 ng/L. The decision limit for MI was set at ≥ 25 ng/L.

Troponin T, used by the other participating hospitals, was analysed by Roche Diagnostic Elecsys 2010, modular analytics E170, Cobas e411, Cobas e601. The 99th percentile upper reference limit was 14 ng/L, with a coefficient variation < 10% at 13 ng/L and a decision limit for MI set at > 14 ng/L.

Cardiac CT protocol

CAC was measured by summing the scores for calcific foci in the coronary arteries, and then expressing the total calcium burden in Agatston units (AU) (10). CAC was assessed by trained radiographers. In an additional 52 subjects the CAC score was reanalysed by the first author.

Two centers used a dual-source CT scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany) with prospective ECG triggering. In participants with a heart rate <75 bpm, ECG triggering was set during the diastolic phase at 65-75% of the cardiac R-R interval, while in persons with a heart rate ≥75 bpm ECG triggering was set during the systolic phase at 250-400 ms. Additional CT settings included the following: sequential prospective scan, slice thickness 3 mm, collimation 128 x 0.6 mm, gantry rotation time 0.28 ms, 120 kV tube voltage, and 90 mAs/rotation.

One center used a GE 64-slice CT-scanner (Discovery 750 HD; GE Healthcare, USA). In individuals with heart rates <75 bpm, ECG triggering was set in diastolic phase at 75% of the cardiac R-R interval, and in those with heart rates ≥75 bpm it was set in the systolic phase at 40% of the cardiac R-R interval. Other settings in this center included: sequential prospective scan, slice thickness 2.5 mm, collimation 64 x 0.625 mm, gantry rotation time 0.35 ms, 120 kV tube voltage, and a 200 mA tube current.

Finally, one center used a Toshiba Aquillion ONE CT scanner (Toshiba Medical systems, Japan) with prospective ECG triggering. If the heart rate was <75 bpm, then ECG triggering was in the diastolic phase at 65%-75% of the R-R interval and if the heart rate was ≥75 bpm then ECG triggering was set in the systolic

phase at 40%. Additional settings were: sequential prospective scan, slice thickness 0.5 mm, collimation 0.5 mm x 240 – 320, gantry rotation time 0.275 ms, and 120 kV tube voltage.

Follow-up

The study was double blinded with a 12 month follow-up. Neither participants nor investigators knew the results of the CAC score until the end of follow-up, at which time participants and their general practitioner received a letter with the results of testing.

The clinical endpoints at follow-up were unstable angina (UAP), non-fatal MI, ventricular tachycardia (VT), coronary revascularization, and cardiac death. The endpoints were compared with the control population and with NSCP patients who were referred for cardiac imaging testing at the index admission, but who consequently did not participate in the study.

Sample size

A sample size calculation was performed before the study. The prevalence of an elevated CAC score (CAC > 0 AU) in the DanRisk comparator population was 44% (15). We assumed that the prevalence of CAC scores in our symptomatic low risk population would be 18% higher (or 62%), since previous studies found that 79% of symptomatic individuals referred for coronary angiography have a CAC > 0 AU (16). Using the Fleiss method, we calculated that we required a sample size of at least 238 patients if we were to detect a risk factor with an OR of at least 2.1, a significance level of 95%, a power of 80%, and a ratio of 1 for exposed/non-exposed.

Statistical analyses

Categorical variables are presented with frequency tables and percentages with the distributions of continuous variables evaluated by empirical histograms. Normally distributed continuous variables are presented as mean and standard deviation (SD) values, whereas skewed distributed continuous variables are presented with their median and interquartile range (IQR). Fischer's exact test and the Chi square test were used for categorical variables, a t-test was used to compare normally distributed variables, and the Wilcoxon's rank sum test was used for skewed distributed variables. NSCP patients and the control population were compared using a multivariate analysis that included traditional CVD risk factors (gender, age, smoking, hypertension, hypercholesterolemia, diabetes mellitus, a family history of CVD, and BMI), the prevalence of CAC (the dependent variable) > 0 and CAC >= 100. The correlation coefficient was 99%. Analyses were performed with STATA SE 14 (StataCorp, College Station, TX, USA). A two-sided P-value < 0.05 was considered statistically significant.

Ethics

The study protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20140055) and conducted in accordance with the Declaration of Helsinki. The study was registered with ClinicalTrials.gov (NCT02422316) and the Danish Data Protection Agency (2008-58-0035 no 1092). Written informed consent was obtained from participating individuals.

The DanRisk protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20080140) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from participating individuals.

Results

In total there were 4,289 patients, 30 to 70 years old, who were seen in either an emergency or cardiology department, and who had at least one troponin measurement. Among these patients, 3,047 were not assessed for study eligibility on the basis of one or more criteria (see Figure 1). Of the remaining 1,241 patients, 800 were assessed for study eligibility, but excluded based on the presence of one or more exclusion criteria. From the residual 441 patients, 229 participated in the study and underwent a cardiac CT scan, while the remaining 212 patients, who were classified as non-participants, either declined study participation or failed to undergo a cardiac CT-scan.

Comparing participants with non-participants, it can be seen that the mean age was respectively 57 years (95% CI; 56-58) and 52 years (95% CI: 50-53), with a p=0.001. Significantly more participants had hypercholesterolemia and a family history of CVD compared with non-participants, while no significant differences were found in gender, diabetes, hypertension, or smoking status (Table 1).

Table 1 : Characteristics of participants and non-participants

	Participants n=229	Non-participants n=212	P-value
Age (years)	57 (56-58)	52 (50-53)	0.001
Male	98 (43)	89 (42)	0.86
Diabetes mellitus	22 (10)	10 (5)	0.048
Hypertension	91 (40)	70 (33)	0.14
Hypercholesterolemia	97 (42)	67 (32)	0.02
Family history	124 (54)	93 (44)	0.03
Smoking	58 (25)	57 (27)	0.71

Values are n (%) or mean (95%CI)

Figure 2 shows the selection of the control group. Of the 1,825 randomly selected individuals 50 or 60 years old who were invited to participate in the DanRisk study, there were 1,257 who accepted the invitation. Based on the criteria established for this study, a total of 535 individuals were excluded from participation, of whom 513 did not fulfill the inclusion criteria of having at least one risk factor, 16 patients had known CAD, and 6 did not have a CAC score. The background comparison group was thus composed of the residual 722 individuals.

Table 2 lists the characteristics of NSCP patients and the background comparison group. Mean age for the NSCP population was 57 years, compared with 55 years for the DanRisk group (p=0.007). A significantly higher proportion of NSCP patients had known hypercholesterolemia and a family history of cardiovascular disease, while more participants in the comparison group were smokers. Furthermore, significant differences were found between the populations with respect to blood pressure, heart rate, and total cholesterol.

Table 2: Descriptive characteristics of Non-Specific Chest Pain patients and the background population.

	NSCP patients n=229 (%)	Background population n=722 (%)	P-value
Male	98 (43)	295 (45)	0.48
Age	57 ±9	55 ±5	0.008
30-39	7 (3)	-	
40-49	46 (20)	-	0.001
50-59	76 (33)	316 (44)	
60-70	100 (44)	406 (56)	
Hypertension	91 (40)	266 (37)	0.460
Hypercholesterolemia	97 (42)	126 (18)	0.001
Diabetes	22 (10)	59 (8)	0.51
Family history of cardiovascular disease	124 (54)	287 (40)	0.001
Smoking	58(25)	314(44)	0.001
Previous smoker	74(32)	197(27)	0.142
Non-smoker	97(42)	211(29)	0.001
Systolic blood pressure (mmHg)	144 ±30	137 ±19	0.001
Diastolic blood pressure (mmHg)	97 ±122	83 ±10	0.002
Heart rate	74 ±14	71 ±14	0.001
Total cholesterol (mmol/L)	5.2 ±1.1	5.5 ±1.1	0.005
LDL cholesterol (mmol/L)	3.1 ±0.9	3.2 ±0.9	0.070
HDL cholesterol (mmol/L)	1.4 ±0.5	1.5 ±0.5	0.080

BMI (kg/m^2)	27 ±6	27 ±5	0.715
CAC score (AU)	2(0:74)	1 (0:54)	0.229
0	106 (46)	350 (48)	0.679
1-99	74(32)	238(33)	0.897
≥ 100	49(22)	134(19)	0.438

Values are n (%), mean ± SD, or median (IQR). NSCP = non-Specific Chest Pain, AU=Agatston unit

The prevalence of the CAC score categories (0 AU, 1-99 AU, ≥100 AU) were similar for the NSCP and background population (46%, 32%, 22% versus 48%, 33%, and 19%, p=0.630), and there was no difference in the median CAC score [2 AU (IQR 0;74 AU) and 1 AU (IQR 0;54 AU), p=0.229]. We analyzed various subgroups, and there were similarly no differences in the median CAC scores for females [0 AU (IQR 0;67 AU) and 0 AU (IQR 0;18 AU), p=0.74], males [18 AU (IQR 0;83 AU) and 9 AU (IQR 0;116 AU), p=0.12], or 50-59 year olds [0 AU (IQR 0;33 AU) and 0 AU (IQR 0;12.5 AU), p=0.25]. However, the subgroup of 60-69 year olds had a higher median CAC score in the NSCP group compared with the background population [47 AU (IQR 0;147 AU) versus 7 AU (IQR 0;110 AU), p=0.008]. In the multivariate logistic regression analysis there was no significant difference in CAC in the NSCP and background population [OR 0.9 (95%CI: 0.6-1.3), p=0.546]. The OR for CAC >100 AU was 1.0 (95% CI:0.6-1.5) p=0.826 (Supplementary Table). In 52 cases, two independent readers performed the CAC score measurement; the Pearson's correlation was 99%.

During one year of follow-up, 2 out of 229 NSCP patients underwent cardiac revascularization, while none had UAP, MI, VT, or death related to cardiac causes. Of the two patients who underwent cardiac revascularization, one was a female age 64 with a CAC score of 340, and the other was a male age 60 years with a CAC score of 2,595. Both were known to have hypertension, hypercholesterolemia, and a significant family history of CVD. The event rate in the background population was 4 out of 722, with all of the involved patients male: two had an MI, one had VT, and one had a cardiac-related death. The patient with VT was 50 years and had a CAC=0, but a significant family history of CVD. The three remaining patients were 60 years old with CAC scores of 166, 832, and 1326. One patient was a smoker with hypertension and hypercholesterolemia, while a second was a smoker with diabetes and a family history of CVD. Fishers exact test showed no statistically difference in the incidence of endpoints between NSCP and the background population [0.9% (95%CI: 0.1-2.9) versus 0.6% (95%CI: 0.2-1.3), p=0.64].

A further 211 patients were referred for cardiac testing at the time of index contact and were not included in this study. Of those, 152 had a cardiac CT, 26 were referred for coronary angiography, and 33 for myocardial perfusion scintigraphy. After one year of follow-up, two of these patients had UAP, two had an

MI, and nine had coronary revascularization. No one had VT or died from cardiac related causes. In total, 11 out of 211 patients [5.2% (95%CI: 2.8-8.9)] had an event, a rate that was significantly higher compared to the NSCP and background populations (p=0.001).

Discussion

This is the first study to our knowledge to evaluate the role of non-contrast CT in an NSCP population.

We demonstrated that CAC can be detected in approximately half of patients with NSCP, a prevalence that does not differ significantly from what can be found in the general population. Furthermore, the prognosis for NSCP patients does not differ from the prognosis in an asymptomatic background population. However, a comparison of NSCP patients and a background population with those referred for cardiac investigation, showed that the latter group has a significantly higher rate of clinical events. As the CAC score in NSCP patients does not differ from the general population, we do not consider non-contrast CT scanning a useful risk stratification tool for NSCP patients. It appears to be of limited value for NSCP patients, and moreover may lead to increased downstream test utilization.

Laudon et al. (17) showed that in non-cardiac chest pain patients presenting to the ED and fulfilling the criteria for UAP, the prevalence of CAC is 49%, which is consistent with our findings in NSCP patients. In Laudon's study, non-cardiac chest pain patients with a CAC=0 had a 100% 5-year probability of event free survival. This was significantly better than for the cardiac related chest pain group, which implies that a non-contrast CT scan may be useful in discriminating between non-cardiac related and cardiac related chest pain. However, the study by Laudon et al. included patients fulfilling the criteria for unstable angina, who were scanned during index contact. Thus, this patient population was at higher risk of CVD compared with the patients in our study, who were not referred for further cardiac investigations after index contact.

The Society of Cardiovascular Computed Tomography Guidelines recommends referring patients for a coronary CT angiography (which also visualizes the arterial lumen) if they present to the emergency department with acute chest pain, a negative ECG, normal biomarkers, a low to intermediate pretest likelihood by risk stratification, and no identifiable coronary cause for their chest pain (18). In the present study, we found that patients who met these guideline criteria had a one-year event rate of 5%, as opposed to the approximately 1% one-year event rate found in NSCP patients for whom a clinical assessment does not suggest a need for additional diagnostic testing. While we did not perform CT angiography, we found that the presence of CAC in NSCP patients did not differ from the background population. Thus, clinical assessments, with respect to risk stratifying NSCP patients for further testing, appear to be accurate. The

differences in characteristics between those referred for further investigations and those included in our study without referral at index contact were not, however, explored in this study.

In our study, it was not possible to reach a conclusion on the prognostic value of CAC in predicting adverse cardiac events, largely due to the small number of study events, the short time to follow-up, and the small number of participants. However, it is worth noting that both of the patients in the NSCP study population who had clinical events had very high CAC scores (349 and 2595), and both had three risk factors for CVD (hypertension, hypercholesterolemia, and a family history of CVD). This finding agrees with previous studies that have demonstrated that a high CAC score is a major and independent CVD risk factor (19). In concordance with previous studies we found a very low event rate in patients without CAC (20). In the NSCP population no cardiac events among patients with a CAC=0 were observed, while one person in the background population had VT and a CAC=0.

The NSCP population included more patients with hypercholesterolemia compared with the background population (43% vs 18%). We know from previous studies that NSCP is associated with frequent contact with the health care system and higher medication use (21). This could partially explain why more patients in this group were diagnosed with hypercholesterolemia.

Strengths /Limitations

The outcome data collected from the Danish registries are well documented and validated, which adds strength to this study (22, 23). The participants in this study and in the background population are likely healthier than the non-participants, with clinical trials involving the latter group demonstrating that they are at higher risk and have worse outcomes (24). The NSCP patients and the background population were preselected to exclude individuals without risk factors as well as those with known CAD or coronary angiography within the last 5 years. Thereby the results are not applicable to very low risk and high risk patients, for whom risk stratification is a less relevant element of care. We know from previous validation studies that the self-reported data for CVD is underreported and inaccurate compared to measured data (25, 26). A sensitivity of 84.5% has been shown for hypertension, hypercholesterolemia, and diabetes (25). This may have influenced the selection of our patients, since the presence of risk factors was an inclusion criteria. Patients who at index admission were referred for further investigations were not included in this study. They could have a higher prevalence of CAC that again would not be accounted for in this study.

The definition of risk factors varied between the study participants and the DanRisk comparator group. Family history was limited by age in the DanRisk study, whereas there was no age limit for NSCP patients. This may explain the higher proportion of patients with a family history of CAD among NSCP patients. Furthermore, the way that data was gathered differed: for NSCP patients the values were extracted from an acute setting, while in contrast the DanRisk patients were investigated in a baseline examination (i.e. the blood pressures were not obtained uniformly and thus not comparable).

The scanners and protocols that were used in the two studies differed, and this may have affected measurements of presence of CAC. However, the centers and scanners used for the CAC assessment in the NSCP patients and background population were almost the same and comparable for that reason.
Finally, the study was underpowered to show any differences in cardiac events. It is thus an observational study characterizing the prevalence of CAC in NSCP patients.

Conclusion

When adjusted for traditional CVD risk factors, the results of this study show that the presence of CAC in NSCP patients does not significantly differ significantly from a background population. Specifically, a little more than half of NSCP patients have detectable CAC on a cardiac CT scan. The prognosis for NSCP patients appears to no worse than a background population with a combined cardiac event rate of less than 1%.

Contributorship

The steering committee (NI, HM, AL, AD, CBM) designed the trial. NI and CBM obtained funding. The investigators (JL, FH, RA, JB, NPS, MHG) trained the staff and gathered data. NI, AD, MHG and CBM analysed the data. NI, CBM, HM, AL and AD wrote the report. All authors can take responsibility for the integrity of the data and the accuracy of the data analysis, and all contributed to the implementation of the study, data interpretation, and approval of the final report for publication.

Data sharing

No additional data is available.

Conflicts of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that: (1) no authors have support from any company for the submitted work; (2) in the previous 3 years no authors had relationships with

companies that might have an interest in the submitted work; (3) no authors have spouses, partners, or children who have a financial relationship that may be relevant to the submitted work; and (4) no authors have non-financial interests that may be relevant to the submitted work.

Figure legends

Figure 1: Flowchart for the inclusion of NSCP patients

Figure 2: Flowchart for inclusion of the background population

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Figure 1: Flowchart for NSCP population inclusion

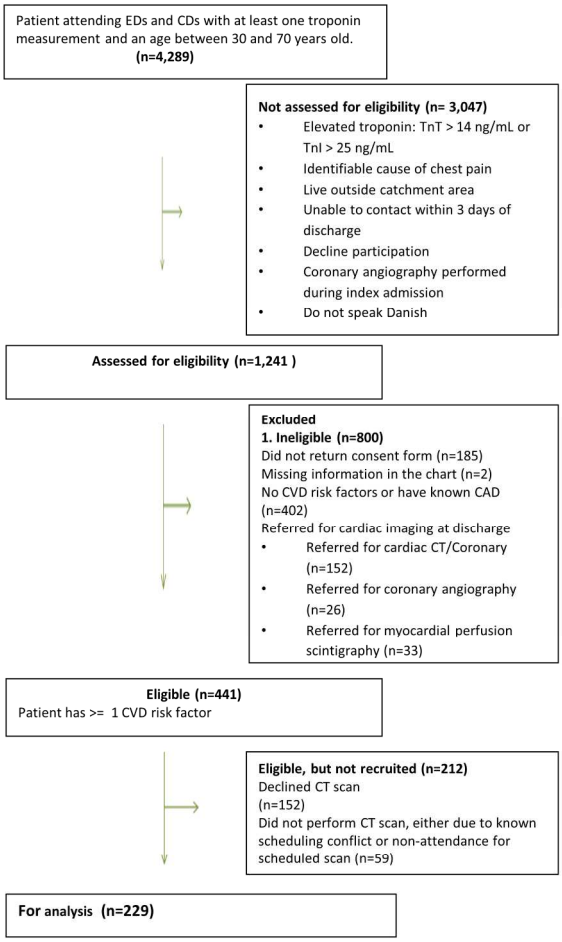

Figure 1: Flowchart for the inclusion of NSCP patients

254x338mm (300 x 300 DPI)

Figure 2: Flow chart for the DanRisk background comparator population

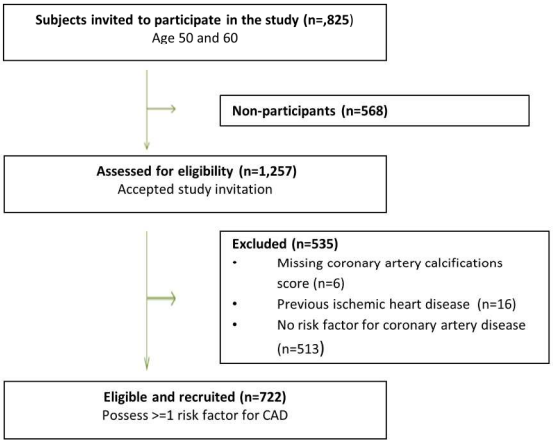

Figure 2: Flowchart for inclusion of the background population

254x338mm (300 x 300 DPI)

Multilogistic regression with B coefficients for CAC above 0 AU

	Coefficient	95% CI
Study population	-0,112	-0.475-0.252
Gender	1.00	0.716-1.291
Age	0.096	0.070-0.121
Current smoker	0.734	0.370-1.098
Previous smoker	0.076	-0.279-0.431
Hypertension	0.324	0.006-0.642
Hypercholesterolemia	0.571	0.221-0.921
Diabetes Mellitus	0.383	-0.137-0.903
Body Mass Index	0.148	-0.189-0.485
Family history of cardiovascular disease	0.257	-0.041-0.554

Multilogistic regression with B coefficients for CAC above 99 AU

	Coefficient	95% CI
Study population	-0.052	-0.516-0.412
Male gender	0.897	0.536-1.258
Age	0.120	0.086-0.154
Current smoker	1.003	0.539-1.468
Previous smoker	0.172	-0.298-0.641
Hypertension	0.755	0.366-1.144
Hypercholesterolemia	0.359	-0.058-0.776
Diabetes Mellitus	0.534	-0.032-1.101
Body Mass Index	-0.026	-0.470-0.417
Family history of cardiovascular disease	0.145	-0.226-0.517

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (Page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page 1)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Page 2)
Objectives	3	State specific objectives, including any prespecified hypotheses (Page 3)
Methods		
Study design	4	Present key elements of study design early in the paper (Page 3)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Page 3-6)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (Page 3-4) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Page 4)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (Page 4-5)
Bias	9	Describe any efforts to address potential sources of bias (Page 6)
Study size	10	Explain how the study size was arrived at (Page 6)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Page 6)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Page 7)
		(*b*) Describe any methods used to examine subgroups and interactions (Page 6-7)
		(*c*) Explain how missing data were addressed (Page 4)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Page 7)
		(b) Give reasons for non-participation at each stage (Page 9)
		(c) Consider use of a flow diagram (Page 9)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Page 10)
		(b) Indicate number of participants with missing data for each variable of interest (None, missing CAC not included in the study)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (Page 12)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (Page 12-13)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (Page 12)
		(*b*) Report category boundaries when continuous variables were categorized (Page 12)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Page 13)
Discussion		
Key results	18	Summarise key results with reference to study objectives (Page 14)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (Page 15)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Page 14-15)
Generalisability	21	Discuss the generalisability (external validity) of the study results (Page 16)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (Page 17)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.