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Subclinical Coronary Atherosclerosis and Risk for Myocardial Infarction in a Danish Cohort

A Prospective Observational Cohort Study

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Background: Coronary atherosclerosis may develop at an early age and remain latent for many years.

Objective: To define characteristics of subclinical coronary atherosclerosis associated with the development of myocardial infarction.

Design: Prospective observational cohort study.

Setting: Copenhagen General Population Study, Denmark.

Participants: 9533 asymptomatic persons aged 40 years or older without known ischemic heart disease.

Measurements: Subclinical coronary atherosclerosis was assessed with coronary computed tomography angiography conducted blinded to treatment and outcomes. Coronary atherosclerosis was characterized according to luminal obstruction (nonobstructive or obstructive [≥50% luminal stenosis]) and extent (nonextensive or extensive [one third or more of the coronary tree]). The primary outcome was myocardial infarction, and the secondary outcome was a composite of death or myocardial infarction.

Results: A total of 5114 (54%) persons had no subclinical coronary atherosclerosis, 3483 (36%) had nonobstructive disease, and 936 (10%) had obstructive disease. Within a median follow-up of 3.5 years (range, 0.1 to 8.9 years), 193 persons died and 71 had myocardial infarction. The risk for myocardial infarction was increased in persons with obstructive (adjusted relative risk, 9.19 [95% CI, 4.49 to 18.11]) and extensive (7.65 [CI, 3.53 to 16.57]) disease. The highest risk for myocardial infarction was noted in persons with obstructive-extensive subclinical coronary atherosclerosis (adjusted relative risk, 12.48 [CI, 5.50 to 28.12]) or obstructive-nonextensive (adjusted relative risk, 8.28 [CI, 3.75 to 18.32]). The risk for the composite end point of death or myocardial infarction was increased in persons with extensive disease, regardless of degree of obstruction—for example, nonobstructive-extensive (adjusted relative risk, 2.70 [CI, 1.72 to 4.25]) and obstructive-extensive (adjusted relative risk, 3.15 [CI, 2.05 to 4.83]).

Limitation: Mostly White persons were studied.

Conclusion: In asymptomatic persons, subclinical, obstructive coronary atherosclerosis is associated with a more than 8-fold elevated risk for myocardial infarction.

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Coronary atherosclerosis is the key pathobiological process responsible for the development of myocardial infarction, which together with a range of both milder and more severe myocardial ischemic manifestations defines the clinical syndrome "ischemic heart disease" (1). Subclinical coronary atherosclerosis precedes ischemic heart disease and may evolve at an early age, many years before clinical disease develops (2, 3). Most knowledge on the natural history of coronary atherosclerosis in humans is derived from observations made in autopsy studies or in persons who have manifested clinical symptoms of coronary atherosclerosis and therefore have had invasive coronary angiography (4–9). For more than 50 years, obstructive coronary artery disease, defined as a luminal coronary stenosis of 50% or greater, has been considered a key feature of elevated risk. In the past decades, however, the extent of atherosclerosis in the coronary tree as well as specific morphologic features of the atherosclerotic plaque have been acknowledged as important risk factors (10, 11).

In the past 20 years, coronary computed tomography angiography (CTA) has been established as a noninvasive test to diagnose obstructive coronary atherosclerosis—equivalent to invasive coronary angiography—and guide treatment strategy in patients presenting with symptoms suggestive of ischemic heart disease (12–15). Furthermore, coronary CTA has proven more sensitive to detect nonobstructive coronary atheroma than invasive coronary angiography (16, 17). Coronary CTA allows for the noninvasive assessment of coronary atherosclerosis, including the severity of luminal obstruction, the extent of disease involvement throughout the coronary vascular tree, and morphologic coronary plaque features by visual assessment (18, 19). The technologic advancements within CT have, furthermore, resulted in high-quality CT images at a very low radiation dose. This technology, therefore,

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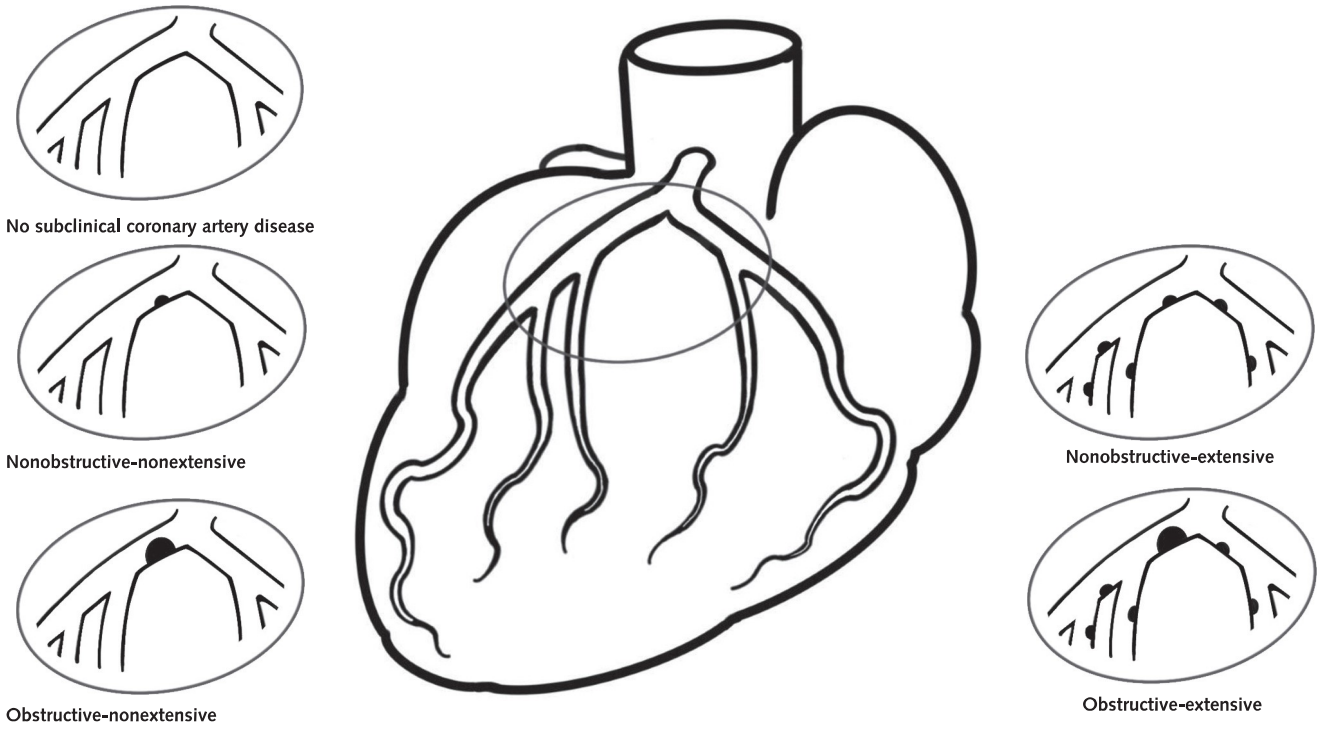
Figure 1. Illustration of combined subclinical coronary atherosclerosis groups by coronary computed tomography angiography.



Coronary luminal diameter atherosclerotic stenosis was categorized on a segment level as nonobstructive (<50% stenosis) or obstructive (≥50% stenosis). Nonextensive disease was defined as atherosclerosis in up to one third of the coronary tree (≤5 coronary segments of 17) and extensive as atherosclerosis in more than one third of the coronary tree (>5 coronary segments of 17). Persons were thus categorized as no atherosclerosis, nonobstructive-nonextensive, nonobstructive-extensive, obstructive-nonextensive, or obstructive-extensive.

provides a unique opportunity to safely assess the relationship between subclinical coronary atherosclerosis and clinical outcome.

We tested the hypothesis that characteristics of subclinical coronary atherosclerosis are associated with an increased risk for myocardial infarction in asymptomatic persons without known ischemic heart disease.

METHODS

Study Design and Participants

The Copenhagen General Population Study (CGPS), initiated in 2003, is a cohort study of persons invited from the greater Copenhagen area, where coronary CTA was added to the research protocol in 2010 (20, 21). From February 2010 and onward, persons in the CGPS could opt for a research coronary CTA examination at Rigshospitalet in Denmark. The Danish National Committee on Biomedical Research Ethics approved the research protocol (H-KF-01-144/01), and all persons provided oral and written consent. Coronary CTA findings remained blinded for both the participant and their physician throughout the follow-up period, as mandated by the ethical committee.

Inclusion criteria to have coronary CTA were age 40 years or older and normal kidney function (serum creatinine, <100 μmol/L [<1.13 mg/dL]). Exclusion criteria for this study were known clinically manifested ischemic heart disease, defined as either previous clinical diagnosis of myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, and, within the past 10 years before inclusion, hospital admittance with suspected unstable angina pectoris, as recorded in the Danish National Patient Registry (International Classification of Diseases, 10th Revision codes I200, I21, and I22) or self-reported chest pain at the time of study inclusion. Participants with coronary CTA evidence of percutaneous coronary intervention or coronary artery bypass graft were also excluded.

Study Procedures

At the time of inclusion, a detailed questionnaire was completed by all participants, including medical history, cardiovascular risk profile, chest pain symptoms, smoking habits, educational-economic factors, and prescribed medication. Furthermore, body metrics were recorded. Overweight was defined as body mass index greater than 25 to less than 30 kg/m^2, and obesity as body mass index 30 kg/m^2 or greater. Office blood pressure was measured according to guidelines, as previously described (22). Hypertension was defined as blood pressure 140/90 mm Hg or greater or prescribed antihypertensive medication. Hypercholesterolemia was defined as low-density lipoprotein 3 mmol/L or greater (116 mg/dL) or prescribed statins. We recorded baseline use of aspirin and statins. Education level was measured in number of years of school. Income class was divided into low

(<$25 000 per year), middle ($25 000 to $80 000 per year), and high income (>$80 000 per year).

Coronary CT Acquisition and Image Analysis

Computed tomography imaging was done using a 320-multidetector scanner (Aquilion ONE ViSION Edition, Canon Medical Systems), and images were evaluated with regards to morphologic characteristics of coronary atherosclerosis, as detailed in the Coronary CTA Methods section of the **Supplement** and **Supplement Table 1** (available at Annals.org).

Subclinical coronary atherosclerosis on a per participant level was categorized according to the absence or presence of obstructive disease (nonobstructive or obstructive) and extent of disease in the coronary tree (nonextensive or extensive). Participants with coronary atherosclerosis were thus categorized into 4 groups: nonobstructive-nonextensive, nonobstructive-extensive, obstructive-nonextensive, and obstructive-extensive (**Figure 1**). Subclinical coronary atherosclerosis according to proximal versus distal location in the coronary vascular tree in addition to high-risk plaque features and coronary artery calcification score (CACS) were also reported (Coronary CTA Methods section of the **Supplement**).

Study End Points

End points were collected from the national Danish Civil Registration System, Danish National Patient Registry, and national Danish Register of Causes of Death. The primary end point was myocardial infarction (International Classification of Diseases, 10th Revision codes I21 and I22). This end point has previously been validated with high validity (23). The secondary end point was a composite of all-cause death or myocardial infarction. Frequency of clinically driven coronary revascularization, as deemed indicated by the responsible treating physicians of the greater Copenhagen area, was also recorded.

Statistical Analysis

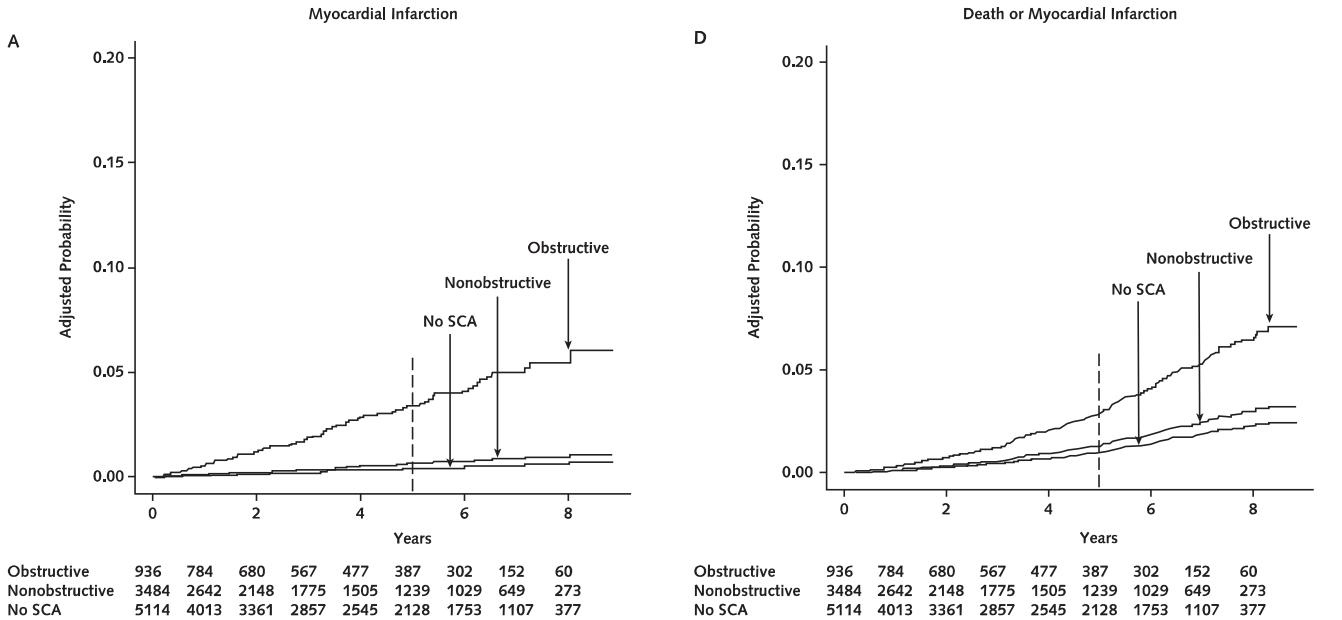
Continuous variables were expressed as mean with 95% CIs in case of approximately symmetrical distribution or median with interquartile range in case of nonsymmetrical distribution. Categorical variables were expressed as frequencies with percentage. Differences of baseline characteristics between groups were assessed by standardized mean differences (values >0.1 suggested potentially meaningful differences). Event rates were calculated as events per 1000 person-years. Adjusted cumulative incidence curves and predicted 5-year risks were calculated using inverse probability weights and presented according to coronary CTA findings. Associations of groups of subclinical coronary atherosclerosis were tested with study end points in Cox proportional hazards regression models and reported as relative risk with 95% CIs in analyses adjusted for sex, age, cardiovascular risk factors (arterial hypertension, hypercholesterolemia, current smoking, overweight or obesity, and diabetes), medication (aspirin and statin), education level, and income class. In the same fashion, associations of coronary plaque characteristics (as defined in **Supplement Table 1**) were tested with the primary and secondary end point in Cox proportional hazards regression models. It was tested if

Table. Clinical Characteristics of the Study Cohort

Characteristic	All	Men	Women	Standardized Mean Difference
Participants, *n*	9533	4089	5444	
Mean age (95% CI), *y*	60.2 (42.7–79.7)	60.3 (42.7–80.6)	60.1 (42.8–79.1)	0.01
Body metrics				
Mean body surface area (95% CI), m^2	1.9 (1.5–2.3)	2.0 (1.8–2.4)	1.8 (1.5–2.1)	1.76
Mean body mass index (95% CI), kg/m^2	25.7 (19.8–34.4)	26.5 (21.2–33.8)	25.3 (19.3–34.7)	0.24
Cardiovascular risk factors, *n* (%)				
Overweight or obesity*	5456 (57)	2793 (68)	2663 (49)	0.28
Hypertension†	3967 (42)	1905 (48)	2062 (38)	0.14
Hypercholesterolemia‡	5679 (60)	2494 (61)	3185 (59)	0.03
Diabetes	175 (2)	99 (2)	76 (1)	0.06
Current smoker	1042 (11)	453 (11)	589 (11)	0.00
Medicine, *n* (%)				
Asprin	632 (7)	311 (8)	321 (6)	0.06
Statin	1015 (11)	489 (12)	526 (10)	0.05
Educational-economic factors				
Mean education level (95% CI), *y*§	11.1 (7.7–14.5)	11.1 (7.6–14.6)	11.1 (7.8–14.5)	−0.01
Income class, *n* (%)‖				0.16
Low	462 (5)	144 (4)	318 (6)	
Middle	3584 (38)	1334 (33)	2250 (41)	
High	5487 (58)	2611 (64)	2876 (53)	

* Overweight or obesity: body mass index >25 kg/m^2.
† Hypertension: ≥140/90 mm Hg or prescribed antihypertensive medication.
‡ Hypercholesterolemia: low density lipoprotein ≥3 mmol/L (116 mg/dL) or prescribed statins.
§ Education level: years of school.
‖ Income class: low: <$25 000 per year, middle: $25 000 to $80 000 per year, high: >$80 000 per year.

Figure 2. Primary and secondary end points.



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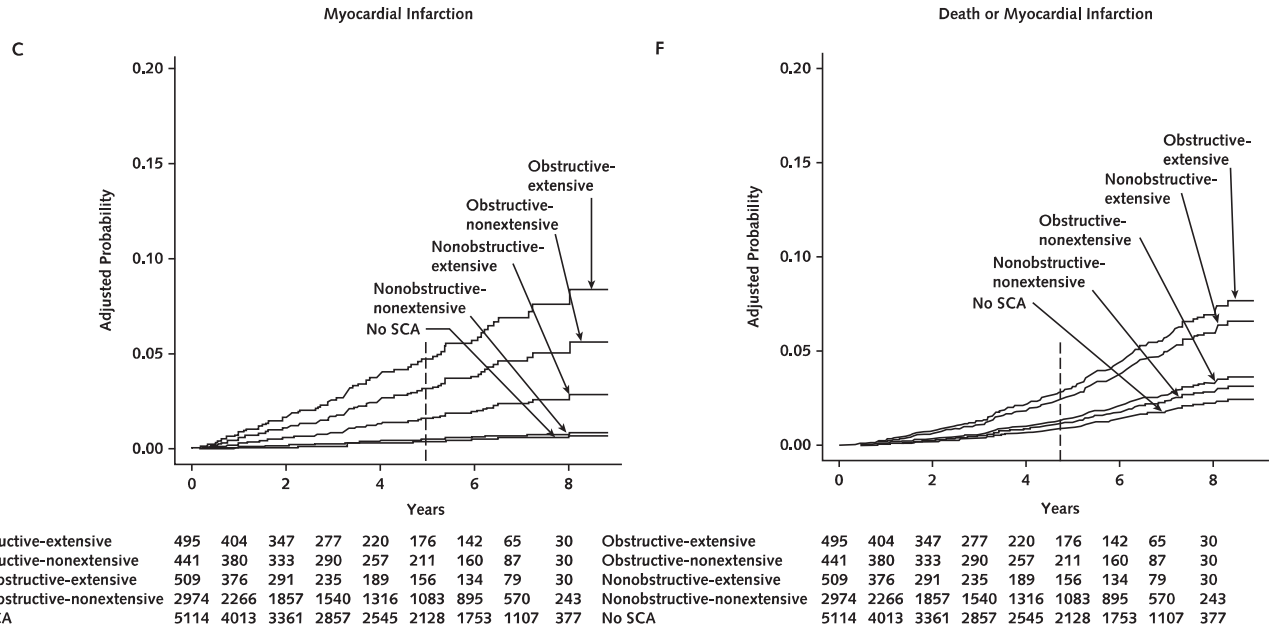
Time to event curves show adjusted probabilities for primary end point of myocardial infarction and secondary composite end point of death or myocardial infarction stratified by CTA findings of SCA. The dotted line indicates 5-y probabilities. Analyses were adjusted for sex, age, arterial hypertension, hypercholesterolemia, current smoking, overweight or obesity, diabetes, aspirin, statin, education level, and income class. CTA = computed tomography angiography; SCA = subclinical coronary atherosclerosis. A and D. Nonobstructive and obstructive. B and E. Nonextensive and extensive. C and F. Combined groups of SCA. For combined groups, plots show increased incidence of myocardial infarction in case of either obstructive-nonextensive or obstructive-extensive SCA (*C*), and increased incidence of either death or myocardial infarction in case of nonobstructive-extensive and obstructive-extensive SCA (*F*).

cardiovascular risk factors modified the association of atherosclerosis with the primary or secondary outcome and reported if the interaction was present. Missing data on baseline characteristics were imputed using median imputation for continuous variables and mode imputation for categorical variables (<7% missing data for any variable). Statistical analysis was done using SAS Enterprise Guide, version 7.1 (SAS Institute), and R, version 4.1.2 (R Foundation for Statistical Computing), with the riskRegression package.

Role of the Funding Source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Figure 2–Continued



Obstructive-extensive	495	404	347	277	220	176	142	65	30
Obstructive-nonextensive	441	380	333	290	257	211	160	87	30
Nonobstructive-extensive	509	376	291	235	189	156	134	79	30
Nonobstructive-nonextensive	2974	2266	1857	1540	1316	1083	895	570	243
No SCA	5114	4013	3361	2857	2545	2128	1753	1107	377

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RESULTS

Characteristics of the Study Cohort

From February 2010 to December 2018, a total of 73 436 persons were included in the CGPS, of whom 12 591 had CT (**Appendix Figure**, available at Annals.org). Known clinically manifested ischemic heart disease or self-reported chest pain was recorded in 1023 (8.1%) persons; these participants were ineligible and excluded from further analysis. Coronary CTA was not available in 1410 participants (11.2%) because of no contrast CT and 625 (5.0%) because of nonevaluable CTA images. This left 9533 eligible participants with a diagnostic CTA in the study cohort. Clinical characteristics of excluded participants are provided in **Supplement Table 2** (available at Annals.org). Eligible participants without CTA were older, more often had obesity, had more cardiovascular risk factors, and were in a lower income class than participants undergoing CTA.

Demographic characteristics, cardiovascular risk factors, medications, and educational-economic characteristics of the participants in the study cohort are provided in the **Table**. More men than women had arterial hypertension, diabetes, hypercholesterolemia, and elevated body mass index, and men had higher income than women. Median radiation dose during noncontrast and contrast CT acquisition was 2.4 mSv (interquartile range, 1.9 to 3.4 mSv).

Coronary CTA Findings

Coronary CTA findings according to obstruction, extent, and combined groups of subclinical coronary atherosclerosis are provided in **Supplement Table 3A** (available at Annals.org). Subclinical coronary atherosclerosis was found in 4419 (46%) of all participants and more frequently in men (n = 2484 [61%]) than in women (n = 1935 [36%]). In the entire population, nonobstructive subclinical coronary atherosclerosis was most frequent (36%), single vessel obstructive disease less frequent (8%), and multivessel disease or left main stenosis rare (2%). The most frequent anatomical location of obstructive disease was observed in the left anterior descending artery. The extent of subclinical coronary atherosclerosis was most frequently nonextensive (36%). The combined subclinical coronary atherosclerosis group nonobstructive-nonextensive was the most frequent (31%). Overall, nonobstructive-nonextensive disease was less frequently found in men than in women. Frequency of coronary high-risk plaque features and CACS groups are shown in **Supplement Table 3B** (available at Annals.org). Spotty calcification was most frequent, followed by noncalcified plaque and napkin-ring sign. In participants with coronary artery calcification, a CACS of 1 to 99 Agatston units was most frequent. Characteristics of participants according to subclinical coronary atherosclerosis findings are shown in **Supplement Tables 4A** to **G** (available at Annals.org).

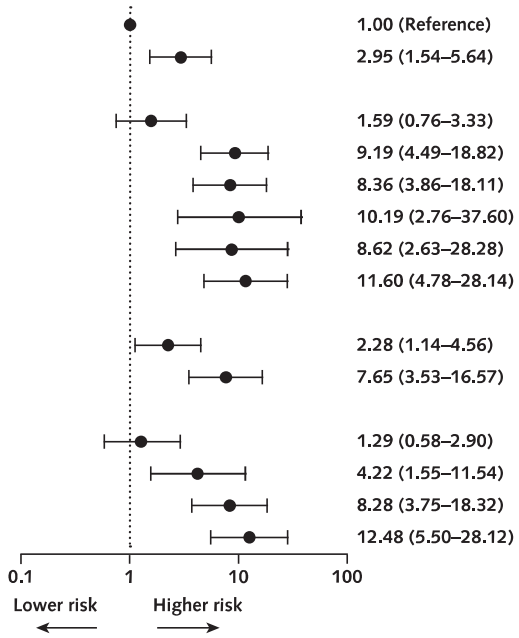
Outcomes and Coronary CTA Findings

Participants were followed for a median of 3.5 years (range, 0.1 to 8.9 years; 39 338 years of cumulated follow-up). During follow-up, 193 participants died and 71 had myocardial infarction, and the secondary composite end points of either death or myocardial infarction occurred in 260. Four persons had myocardial infarction and died.

The risk for myocardial infarction according to coronary CTA findings is shown in **Figure 2** (*A* to *C*), **Figure 3**, and **Supplement Table 5** (available at Annals.org). Both

Figure 3. Adjusted 5-year probabilities, risk differences, and relative risks for myocardial infarction according to coronary CTA findings of subclinical coronary atherosclerosis.

CTA Findings	Mean Adjusted 5-Year Probabilities (95% CI)	Mean Risk Difference, %	Mean Relative Risk (95% CI)
No subclinical coronary atherosclerosis	0.36 (0.16–0.76)	– (Reference)	1.00 (Reference)
Any subclinical coronary atherosclerosis	1.02 (0.55–1.89)	0.67	2.95 (1.54–5.64)
Obstructive subclinical coronary atherosclerosis			
Nonobstructive	0.59 (0.30–1.17)	0.23	1.59 (0.76–3.33)
Obstructive	3.40 (1.68–6.89)	3.04	9.19 (4.49–18.82)
LAD obstructive (1VD)	3.07 (1.47–6.43)	2.71	8.36 (3.86–18.11)
Cx obstructive (1VD)	3.75 (0.84–16.63)	3.39	10.19 (2.76–37.60)
RCA obstructive (1VD)	3.17 (0.94–10.72)	2.81	8.62 (2.63–28.28)
Multi-VD/LM-obstructive	4.26 (1.86–9.78)	3.90	11.60 (4.78–28.14)
Extent of subclinical coronary atherosclerosis			
Nonextensive	0.84 (0.44–1.62)	0.49	2.28 (1.14–4.56)
Extensive	2.83 (1.33–5.98)	2.48	7.65 (3.53–16.57)
Combined groups of subclinical coronary atherosclerosis			
Nonobstructive-nonextensive	0.49 (0.22–1.08)	0.13	1.29 (0.58–2.90)
Nonobstructive-extensive	1.60 (0.64–4.00)	1.24	4.22 (1.55–11.54)
Obstructive-nonextensive	3.13 (1.47–6.67)	2.77	8.28 (3.75–18.32)
Obstructive-extensive	4.71 (2.11–10.53)	4.35	12.48 (5.50–28.12)



Analyses were adjusted for sex, age, arterial hypertension, hypercholesterolemia, current smoking, overweight or obesity, diabetes, aspirin, statin, education level, and income class. 1VD = single vessel disease; CTA = computed tomography angiography; Cx = circumflex artery; LAD = left anterior descending artery; LM = left main artery; RCA = right coronary artery; VD = vessel disease.

obstructive and extensive subclinical coronary atherosclerosis were associated with an increased risk for myocardial infarction, as compared with participants without atherosclerosis. The elevated risk associated with obstructive disease was found to be unrelated to location in the vessel, with elevated risk in both proximal and distal lesions (**Supplement Table 6**, available at Annals.org). For the combined groups of subclinical coronary atherosclerosis, the risk for myocardial infarction was more than 8-fold increased in participants with either obstructive-nonextensive (adjusted relative risk, 8.28 [95% CI, 3.75 to 18.32]) or obstructive-extensive subclinical coronary atherosclerosis (adjusted relative risk, 12.48 [CI, 5.50 to 28.12]), as compared with participants without atherosclerosis.

Any coronary high-risk plaque feature (spotty calcification, napkin-ring sign, or noncalcified plaque), each high-risk plaque feature, and groups of CACS were associated with risk for myocardial infarction in a multivariable Cox model adjusted for risk factors (**Supplement Table 6**).

The risk for the secondary composite end point of either death or myocardial infarction according to coronary CTA findings is shown in **Figure 2** (*D* to *F*), **Figure 4**, and **Supplement Tables 7** and **8** (available at Annals.org). Both obstruction and extent of subclinical coronary atherosclerosis were associated with an increased risk for death or myocardial infarction as compared with participants without atherosclerosis. For combined groups of subclinical coronary atherosclerosis, the risk for death or myocardial infarction was more than doubled in participants with either nonobstructive-extensive (adjusted relative risk, 2.70 [CI, 1.72 to 4.25]) or obstructive-extensive subclinical coronary atherosclerosis (adjusted relative risk, 3.15 [CI, 2.05 to 4.83]), as compared with participants without atherosclerosis.

No cardiovascular risk factors interacted with any coronary atherosclerosis to modify neither risk for myocardial infarction nor risk for death or myocardial infarction, although no interaction analysis was possible for persons with diabetes because of lack of events.

The risk for undergoing clinically driven coronary revascularization according to CTA findings is shown in the **Supplement Figure** (available at Annals.org). In all participants with subclinical coronary atherosclerosis, the risk for undergoing coronary revascularization was increased, with the highest risk noted in participants with obstructive-extensive subclinical coronary atherosclerosis.

DISCUSSION

Among asymptomatic, middle-aged persons without known ischemic heart disease, we have shown that subclinical coronary atherosclerosis may be found in more than half of men and one third of women. Although the most common type of subclinical disease was nonobstructive and/or nonextensive coronary atherosclerosis, obstructive atherosclerosis was present in 10% of the study cohort. Obstructive subclinical coronary atherosclerosis

was associated with a more than 8-fold increased risk for myocardial infarction, and the risk for either death or myocardial infarction was increased 2-fold in persons with extensive subclinical coronary atherosclerosis.

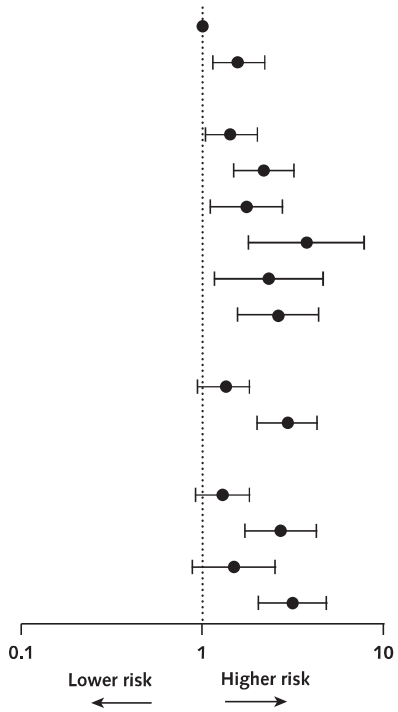
Throughout the entire follow-up period, coronary CTA findings remained clinically blinded, as mandated by the ethical committee. This ruling of the ethical committee was to avoid any intervention based on CTA findings not supported by scientifically based clinical guidelines. Our observations, therefore, reflect the natural history of subclinical coronary atherosclerosis in the setting of medical and lifestyle risk modifications according to contemporary clinical practice.

Two previous large-scale studies—the FACTOR-64 trial (Screening For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography, Following Core 64) and SCAPIS (Swedish CArdioPulmonary bioImage Study)—reported the prevalence of subclinical coronary atherosclerosis (24, 25). The FACTOR-64 trial examined, in a randomized design, persons with diabetes, and the reported prevalence of subclinical coronary artery disease was consistent with the prevalence in similar persons with diabetes in our CGPS cohort (FACTOR-64: 69% vs. CGPS: 70%). Importantly, as part of the FACTOR-64 study design, all persons undergoing CTA had subsequent coronary intervention guided by CTA findings. In a transverse observational design not reporting outcome, SCAPIS examined persons aged 50 to 64 years in the general population of Sweden and when compared with the subgroup of participants with similar age in the CGPS cohort, we found a similar proportion of persons with subclinical coronary atherosclerosis (SCAPIS: 42% vs. CGPS: 41%).

In one of the early reports on the use of invasive coronary angiography in symptomatic persons by Abrams and Adams in 1969 (26), it was stated that a "luminal narrowing of at least 50% can be considered clinically serious." Subsequently, this notion—that luminal coronary obstruction is a major risk factor for the development of serious disease, including myocardial infarction—developed into the ruling paradigm of the field. However, as reviewed by Libby in 2013 (3), the natural history of coronary atherosclerosis is influenced by multiple inflammatory and clonal hematopoietic pathways, which may offset the pathogenetic importance of luminal coronary stenosis severity. Furthermore, studies using coronary artery calcium scoring by CT as a marker of coronary atherosclerotic burden in both asymptomatic and symptomatic persons have shown that the extent of vascular calcification is an important indicator of elevated risk (27, 28). In our CGPS study in asymptomatic healthy persons without

Figure 4. Adjusted 5-year probabilities, risk differences, and relative risks for death or myocardial infarction according to coronary CTA findings of subclinical coronary atherosclerosis.

CTA Finding	Mean Adjusted 5-Year Probability (95% CI)	Mean Risk Difference, %	Mean Relative Risk (95% CI)
No subclinical coronary atherosclerosis	0.95 (0.65–1.37)	– (Reference)	1.00 (Reference)
Any subclinical coronary atherosclerosis	1.50 (1.04–2.16)	0.55	1.59 (1.16–2.20)
Obstructive subclinical coronary atherosclerosis			
Nonobstructive	1.37 (0.94–2.00)	0.42	1.44 (1.03–2.00)
Obstructive	2.08 (1.34–3.21)	1.13	2.18 (1.48–3.20)
LAD obstructive (1VD)	1.67 (1.01–2.75)	0.72	1.74 (1.10–2.77)
Cx obstructive (1VD)	3.62 (1.67–7.87)	2.67	3.78 (1.83–7.83)
RCA obstructive (1VD)	2.24 (1.06–4.71)	1.29	2.34 (1.16–4.70)
Multi-VD/LM-obstructive	2.50 (1.46–4.29)	1.55	2.61 (1.56–4.36)
Extent of subclinical coronary atherosclerosis			
Nonextensive	1.31 (0.90–1.92)	0.36	1.32 (0.94–1.85)
Extensive	2.91 (1.88–4.50)	1.96	2.93 (1.99–4.31)
Combined groups of subclinical coronary atherosclerosis			
Nonobstructive-nonextensive	1.28 (0.87–1.90)	0.33	1.29 (0.91–1.83)
Nonobstructive-extensive	2.69 (1.66–4.37)	1.74	2.70 (1.72–4.25)
Obstructive-nonextensive	1.49 (0.84–2.63)	0.54	1.49 (0.88–2.54)
Obstructive-extensive	3.14 (1.94–5.06)	2.19	3.15 (2.05–4.83)



Analyses were adjusted for sex, age, arterial hypertension, hypercholesterolemia, current smoking, overweight or obesity, diabetes, aspirin, statin, education level, and income class. 1VD = single vessel disease; CTA = computed tomography angiography; Cx = circumflex artery; LAD = left anterior descending artery; LM = left main artery; RCA = right coronary artery; VD = vessel disease.

known ischemic heart disease, we found that both coronary extent and the presence of obstructive luminal stenosis were independently associated with an increased risk for myocardial infarction, albeit with the highest risk found in persons with obstructive disease. Our findings suggest that a superimposed luminal thrombus may occur in both nonobstructive and obstructive atherosclerotic lesions, leading to acute myocardial infarction. In the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study, which studied the natural history of coronary atherosclerosis using intravascular ultrasound, the highest risk for recurrent events was noted in patients with lesions characterized by a small luminal area and a high focal lesion plaque burden (8). In both the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial and the SCOT-HEART (Scottish COmputed Tomography of the HEART) trial, it was found that patients with obstructive coronary artery disease had a higher likelihood of having coronary heart disease death or myocardial infarction than patients with nonobstructive disease (29, 30). Overall, these previous results in symptomatic patients seem to be in concordance with our finding that the highest risk for acute myocardial infarction was found in persons with obstructive disease. Interestingly, we found that obstructive disease both in proximal and distal coronary segments was associated with an elevated risk for myocardial infarction, suggesting that obstruction per se and to a lesser degree anatomical location, is an important feature of elevated risk.

Both noncontrast coronary artery calcium scoring and high-risk plaque features defined by visual coronary CTA analysis were each independently associated with elevated risk for acute myocardial infarction. An important topic of investigation is to assess the clinical usefulness of coronary CTA as compared with noncontrast coronary artery calcium scoring for the assessment of risk in asymptomatic persons. However, this was outside the scope of the current work. In future studies, it will also be of substantial interest to assess the individual contributions of atherosclerotic morphologic characteristics of coronary calcification, extent, luminal obstruction, and segmental and total plaque burden, in addition to high-risk plaque features, including positive remodeling to overall cardiovascular risk. Importantly, this will most likely require implementation of quantitative coronary CTA, potentially deep learning based, image analysis tools (19, 31, 32).

In 14 participants with no subclinical coronary atherosclerosis at baseline (0.2%), a myocardial infarction occurred during a median follow-up of 3.5 years. This observation highlights that the mechanism and velocity of de novo development and subsequent progression of coronary atherosclerosis in asymptomatic persons is poorly defined. On the other hand, disease entities with angiographically normal coronary arteries, such as spontaneous coronary artery dissection, Takotsubo cardiomyopathy, and coronary microvascular disease, in addition to type 2 myocardial infarction and/or false-negative coronary CTA readings, may be responsible for this finding. Overall, our findings have important implications for the basic pathophysiologic understanding of how subclinical coronary atherosclerotic disease progresses to clinically manifested disease and define a foundation for novel strategies of primary cardiovascular prevention.

In the public health classic *Principles and Practice of Screening for Disease* by Wilson and Jungner (33), published in 1968 by the World Health Organization, a list of 10 criteria was suggested that should be met for screening programs to be meaningful and worthwhile. Most of these criteria seem now to be met, supporting screening for subclinical coronary atherosclerosis using coronary CTA. However, 1 essential, unanswered question remains before a systematic, generalized coronary CTA screening program can be recommended: Does preventive treatment guided by coronary CTA reduce the risk for heart attacks or death and avoid harm to persons not in need of treatment as compared with current primary cardiovascular prevention practice? To answer this question, we have initiated a randomized controlled trial—the DANE-HEART (Computed Tomography Coronary Angiography for Primary Prevention; ClinicalTrials.gov: NCT05677386) trial—in which 6000 asymptomatic persons at risk for ischemic heart disease will be randomly assigned to primary preventive treatment guided by coronary CTA or current primary prevention practice. Preventive treatment in the coronary CTA guided group of our trial will be done according to groups of subclinical coronary luminal obstruction and extent of atherosclerotic disease by coronary CTA as defined in this report. Nevertheless, while waiting for the results of the DANE-HEART trial as well as those of the SCOT-HEART 2 trial (Computed Tomography Coronary Angiography for the Prevention of Myocardial Infarction; ClinicalTrials.gov: NCT03920176) that is being done in parallel, it would be prudent to consider possible clinical implications of our findings in the setting of opportunistic screening. Identification of luminal obstructive or extensive subclinical coronary atherosclerosis, which we have shown are associated with high risk, provides potentially clinically relevant, incremental risk assessment in patients without suspected or known ischemic heart disease undergoing cardiac CT and/or electrocardiogram-gated chest CT for other clinical indications. This could apply in patients having electrocardiogram-gated chest CT for procedural planning before atrial fibrillation ablation, left atrial appendage closure, and invasive treatment of heart valve disease, in addition to patients examined for suspected aortopathy (34). Such patients with obstructive and/or extensive subclinical coronary atherosclerosis could benefit from referral to intensified cardiovascular primary prevention therapy.

This study has some limitations. Participants of the CGPS mostly consist of White persons from the Nordic European region and our findings may therefore not apply in other populations. Furthermore, persons undergoing coronary CTA in the CGPS tended to have less cardiovascular

risk factors, higher education level, and higher income class. In this work, coronary CTA was assessed using visual assessment, not including quantitative CT, which could have provided more detailed morphologic assessment of coronary plaque (31, 32). Finally, information on myocardial infarction anatomical location and specific causes of death during follow-up were not available. Our results should therefore be interpreted accordingly.

In conclusion, in asymptomatic middle-aged persons of the background population without known ischemic heart disease, obstructive subclinical coronary atherosclerosis has the highest risk for subsequent development of myocardial infarction.

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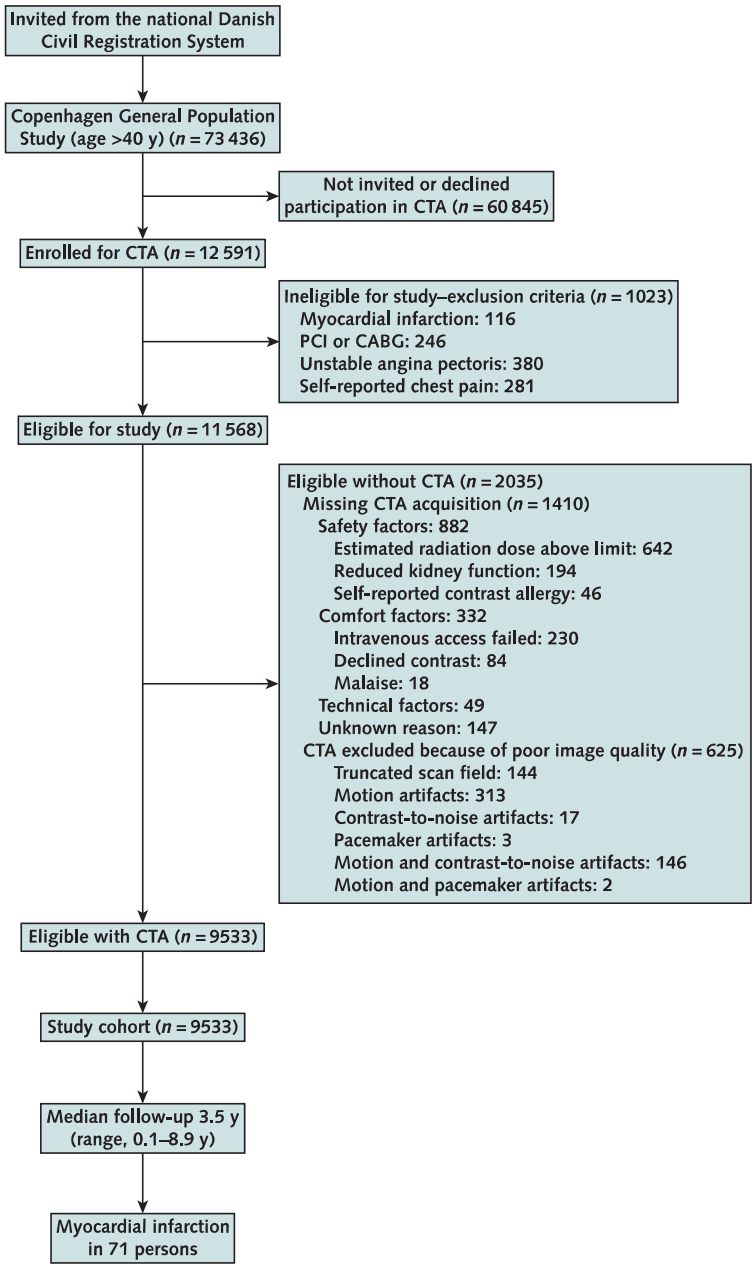
Appendix Figure. Flow chart.



CABG = coronary artery bypass graft; CTA = computed tomography angiography; PCI = percutaneous coronary intervention.