Five-Year Outcomes After Coronary Computed Tomography Angiography (From 110,599 Patients in a Danish Nationwide Register-Based Follow-Up Study)

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The long-term cardiovascular risk for patients examined with coronary computed tomography angiography (CCTA) to rule out coronary heart disease compared with population controls remains unexplored. A nationwide register-based study including first-time CCTA-examined patients between 2007 and 2017 in Denmark alive 180 days post-CCTA was conducted. We evaluated 5-year outcomes of myocardial infarction (MI) or revascularization and all-cause mortality in 3 distinct CCTA-groups: (1) no post-CCTA preventive pharmacotherapy use (cholesterol-lowering drugs, antiplatelets, or anticoagulants); (2) post-CCTA preventive pharmacotherapy use; and (3) revascularization or MI within 180 days post-CCTA. For each patient group, population controls were matched on age, gender, and calendar year. Absolute risks standardized to the age, gender, selected comorbidity, and anti-anginal pharmacotherapy distributions of the specific CCTA-examined patients and respective controls were obtained from multivariable Cox regression. Of 110,599 CCTA-examined patients, (1) 48,231 patients were not prescribed preventive pharmacotherapy 180 days post-CCTA; (2) 42,798 patients were prescribed preventive pharmacotherapy within 180 days post-CCTA; and (3) 19,570 patients were diagnosed with MI or revascularized within 180 days post-CCTA. For patient groups 1 to 3 versus respective controls, 5-year MI or revascularization risks were <0.1% versus 2.0%, <0.1% versus 3.8%, and 19.0% versus 2.5%, all p<0.001. Five-year all-cause mortality were 2.8% versus 4.2%, 5.5% versus 8.8%, and 6.7% versus 8.5%, all p <0.001. In conclusion, the 5-year MI or revascularization risk can be considered very low for CCTA-examined patients without ischemic events within 180 days post-CCTA. Conversely, CCTA-examined patients with MI or revascularization events within 180 days post-CCTA have significantly elevated 5-year MI or revascularization risk. **(Am J Cardiol 2022;176:1−7)**

Introduction

Coronary computed tomography angiography (CCTA) has a high accuracy of coronary artery disease (CAD) detection with a direct impact on treatment, decision making, and prognosis.[1,2] On this basis, societal guidelines recommend CCTA as a frontline test for patients with unexplained chest pain and without known CAD.[3−12] In the recent SCOT-HEART trial, patients investigated with CCTA, in addition to standard care, demonstrated an important reduction in cardiovascular death or nonfatal myocardial infarction (MI), likely driven by improved CAD diagnosis and initiation of preventive treatment of nonobstructive CAD diagnosed by CCTA.[1] Data on long-term cardiovascular risk concerning preventive pharmacological treatment measures and other intervention strategies post-CCTA compared with the background population is sparse. Such an investigation can provide a better understanding of the prognostic value of real-world CCTA testing in patients suspected of CAD. Therefore, in a large nationwide register-based study, we examined long-term clinical outcomes in patients who underwent first-line CCTA in comparison to age-matched and gender-matched background population controls.

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See page 6 for disclosure information.

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Methods

This nationwide registry-based study includes patients who underwent first-time CCTA testing in Denmark between 2007 and 2017. In Denmark, CCTA has emerged as the preferred first-line test in patients with suspected CAD.[13] Age-matched, gender-matched, and calendar year-matched controls (matched on a 1:2 basis) were derived from the background population. Both CCTA-examined patients and controls with known CAD before the CT examination were excluded. The nationwide registries used in this study included information on the date of the CCTA examination, but no granular data on the test result was available. Consequently, we differentiated post-CCTA patients being alive 180 days post-CCTA into 3 distinct post-CCTA categories based on preventive pharmacotherapy use (cholesterol-lowering drugs, antiplatelets, or anticoagulants) and ischemic events within 180 days post-CCTA:

1) no post-CCTA preventive pharmacotherapy use (low-risk group);

2) post-CCTA preventive pharmacotherapy use (moderate to higher risk group), and

3) revascularization or MI within 180 days post-CCTA (high to very high-risk group).

Patients in group 1 most likely did not have any significant CAD as secondary prevention medication was not prescribed within 180 days post-CCTA and were therefore classified as low risk. In contrast, patients in group 2 (moderate to higher risk) and group 3 (high to very high risk) were classified as having significant CAD with an indication for secondary preventive medication use. For group 3, patients were, in addition, diagnosed with MI or revascularized within 180 days post-CCTA. For each of these patient groups, population controls were matched on age, gender, and calendar year.

All residents in Denmark are given a civil personal registration number upon birth or immigration, and this unique identifier is stored in the Danish Civil Registration System, from which we also include the date of birth, gender, and vital status.[14] The civil personal registration number is used in all healthcare contacts and contacts with social and governmental bodies in Denmark. All medical procedures and diagnoses related to hospital and outpatient contacts are available from the Danish National Patient Register.[15] In addition to all incident CCTA procedures from 2007 to 2017 in Denmark, we also included information on downstream functional testing in the first 180 days post-CCTA, including cardiac magnetic resonance with myocardial perfusion imaging, positron emission tomography, nuclear stress testing, and invasive coronary angiography and revascularization procedures in the same time span. Revascularization was defined as either percutaneous intervention or coronary artery bypass grafting. Pharmacotherapies prescribed before and after CCTA were assessed from the Danish National Prescription Registry.[16]

Antiplatelet therapy use in CCTA-examined patients was defined as either aspirin or P2Y12 inhibitor use and anticoagulant therapy as either vitamin K antagonist or direct oral anticoagulant use using data from the Danish National Prescription Registry. Cholesterol-lowering drug use was defined as any lipid-modifying drug, including statins, PCSK9 inhibitors, fibrates, bile acid sequestrants, niacin, selective cholesterol absorption inhibitors, omega 3 fatty acids and fatty acid esters, and adenosine triphosphate-citrate lyase inhibitors. Information on hypertension, diabetes mellitus, chronic kidney disease (CKD), atrial fibrillation or flutter (AF), heart failure (HF), and chronic obstructive pulmonary disease (COPD) were also retrieved from the Danish National Patient Register. We included relevant diagnoses within the last 5 years before 180 days post-CCTA. In addition, we used information on antihypertensive drugs, antidiabetics, and selected inhalation drugs (anticholinergic and long-acting beta-agonists) to define hypertension, diabetes mellitus, and COPD, respectively. For diabetes mellitus and COPD, relevant prescription medication within the 180 days post-CCTA was considered. For the definition of hypertension using antihypertensive drugs, at least 2 antihypertensive drug redemptions in 2 consecutive quarters (both the 180-day post-CCTA period and an additional 180 days before that period) were required, as done previously.[17,18] Anti-anginal pharmacotherapy use, including nitrates, β-blockers, and calcium-antagonists, was in addition assessed within the 180 days post-CCTA. Information on vital status, causes of death, and diagnoses to construct the study end points as specified later were retrieved from the Danish Civil Registration System, the Danish National Cause of Death Register, and the Danish National Patient Registry.[14,15,19]

End points were (1) all-cause mortality, (2) MI, (3) composite of MI or revascularization, and (4) composite of MI, revascularization, or all-cause mortality. The MI definition included both MI-related fatal and nonfatal events. In addition to all-cause mortality, we also reported presumed cardiovascular (CV) death. To avoid immortal time bias, we included only the time passed after the post-CCTA test treatment window (0 to 180 days after the CCTA examination) in our event estimation. Patients were followed for 5 years or until first event of interest, competing event of non−MI-related death, or end of study on December 31, 2018, whichever came first.

Continuous data are reported using medians and 25 to 75 percentiles [Q1-Q3: first to third quartiles], and categorical data using counts and percentages. Outcomes of all-cause mortality and composite end point of MI, revascularization, and all-cause mortality are reported using Kaplan-Meier estimates. Outcomes of MI, including fatal MI, and composite end point of MI, including fatal MI or revascularization, are reported using cumulative incidences, treating non −MI-related causes of mortality as competing risks. Multivariable Cox regression was used to derive absolute and relative risks, standardizing the outcome risks to the age, gender, selected co-morbidity, and pharmacotherapy distributions of the specific patient category group and the respective control group. Standardization was used to ensure that patients and controls have similar age, gender, selected co-morbidity, and pharmacotherapy distributions

to examine the impact of the post-CCTA treatment group on outcomes. The multivariable model included the following covariates: age, gender, hypertension, diabetes mellitus, CKD, AF, HF, COPD, nitrate, β-blocker, and calcium antagonist use. Data management and statistical analyses were performed using SAS, Version 9.4 (Cary, North Carolina), and R Software Version 4.0.3. (The R Foundation for Statistical Computing, Vienna, Austria).[20]

In Denmark, register-based studies do not require informed consent or ethical approval. The use of the data sources for the present study is approved by the data responsible institute in the Capital Region of Denmark (approval No. P-2019-404) in accordance with the General Data Protection Regulation.

Results

From 2007 to 2017, a total of 128,777 incident CCTA examinations were identified. Of these, 17,417 patients had pre-existing CAD before the CCTA examination and were excluded. In addition, 761 patients died within the first 180 days and were also excluded, leaving a CCTA study population of 110,599 eligible for further analysis. The median follow-up was 3.8 years. In total, the study population comprised: (1) 48,231 patients who were not prescribed preventive pharmacotherapy 180 days post-CCTA; (2) 42,798 patients were prescribed preventive pharmacotherapy within 180 days post-CCTA, and (3) 19,570 patients were diagnosed with MI or revascularized within 180 days post-CCTA.

Characteristics of CCTA-examined patients for each patient group (1-3), compared to respective controls, are listed in Table 1. The age distributions were 54, 64, and 63 years for patient groups 1 to 3 and their respective controls. Fewer men than women were represented in group 1, whereas patients were more likely of male gender in groups 2 and 3. Co-morbidities including hypertension, CKD, AF, HF, and COPD were more frequent in CCTA-examined patients relative to respective controls. For diabetes mellitus, the distribution between the patient group and the respective controls was equal. In contrast, the diabetes mellitus prevalence was significantly higher in patients in groups 2 and 3 relative to their respective controls. Distributions of pharmacotherapy use before and after CCTA for CCTA-examined patients (groups 1 to 3) versus respective controls are listed in Table 2.

A total of 761 (0.6%) CCTA-examined patients died within the first 180 post-CCTA days. When compared with the CCTA-examined patients who survived the first 180 days post-CCTA, the 761 patients who died within this time frame were older and had more co-morbid conditions, including hypertension, diabetes mellitus, CKD, AF, HF, COPD, and more frequent use of P2Y12 inhibitors and anticoagulants before CCTA, whereas distributions of gender and use of aspirin and cholesterol-lowering drugs before CCTA were comparable (Supplementary Table 1).

The use of downstream functional testing and invasive coronary angiography use within 180 days post-CCTA are listed in Supplementary Table 2. The use of invasive coronary angiography within 180 days post-CCTA was 1.9%, 11.1%, and 69.5% for patient groups 1 to 3 versus 0.1% in all control groups (all $p < 0.001$). The revascularization to invasive coronary angiography ratio in patient group 3 (the only group in whom revascularization was performed within 180 days post-CCTA) was 0.54.

Crude Kaplan-Meier curves for all-cause mortality and composite end point of MI or revascularization or all-cause mortality and crude cumulative incidences of MI, including fatal MI and MI or revascularization, are shown in Supplementary Figures 1 to 3. Standardized absolute risks of 5-year all-cause mortality were significantly lower for patient groups 1 to 3 than for respective controls: 2.8% versus 4.2%, 5.5% versus 8.8%, and 6.7% versus 8.5%, all $p < 0.001$ (Figure 1, Supplementary Table 3). The standardized absolute risks for presumed CV death for groups 1 to 3 versus respective controls were 0.4% versus 0.7% ($p < 0.001$), 1.1% versus 1.5% ($p < 0.001$), and 2.0% versus 2.2% ($p = 0.40$). For patient groups 1 to 2 relative to their respective control groups, standardized 5-year ischemic events were significantly lower for all CCTA-examined patients, with MI or revascularization risks for groups 1 versus respective controls of <0.1% versus 2.0% and group 2 versus respective controls of <0.1% versus 3.8%. Only patient group 3 consisting of CCTA-examined patients who

Table 1
Clinical risk profiles of CCTA-examined patients (Groups 1 to 3) versus respective controls

Variable n	Patient Group 1 n=48,231	Controls n=96,462	Patient Group 2 n=42,798	Controls n=85,596	Patient Group 3 n=19,570	Controls n=39,140
Age, years	54 [46−63]	54 [46−63]	64 [56−70]	64 [56−70]	63 [55−70]	63 [55−70]
Men	22,361 (46.4%)	44,722 (46.4%)	23,084 (53.9%)	46,168 (53.9%)	11,037 (56.4%)	22,074 (56.4%)
Hypertension	4,049 (8.4%)	3,357 (3.5%)	8,288 (19.4%)	4,796 (5.6%)	3,729 (19.1%)	2,034 (5.2%)
Diabetes	573 (1.2%)	1,132 (1.2%)	1,915 (4.5%)	1,524 (1.8%)	684 (3.5%)	589 (1.5%)
Chronic kidney Disease	178 (0.4%)	268 (0.3%)	422 (1.0%)	426 (0.5%)	162 (0.8%)	184 (0.5%)
Atrial fibrillation or Flutter	812 (1.7%)	698 (0.7%)	3,804 (8.9%)	1,262 (1.5%)	732 (3.7%)	527 (1.3%)
Heart failure	806 (1.7%)	356 (0.4%)	2,050 (4.8%)	591 (0.7%)	693 (3.5%)	231 (0.6%)
Chronic obstructive pulmonary disease	888 (1.8%)	800 (0.8%)	1,256 (2.9%)	1,086 (1.3%)	623 (3.2%)	423 (1.1%)

Patient groups 1-3 refer to: (1) no post-CCTA preventive pharmacotherapy use (cholesterol-lowering drugs, antiplatelets or anticoagulants);
(2) post-CCTA preventive pharmacotherapy use; and 3) revascularization or MI within 180 days post-CCTA. Controls are derived from the background population matched on age, gender and calendar year. Continuous variables are presented using median and Q1-Q3, categorical variables using numbers and percentages.

CCTA = coronary computed tomography angiography; n = number; Q1-Q3 = first to third quartiles.

Table 2
Before versus after CCTA medication for patient Groups 1 to 3 versus respective controls

Variable n	Patient Group 1 n=48,231	Controls n=96,462	Patient Group 2 n=42,798	Controls n=85,596	Patient Group 3 n=19,570	Controls n=39,140
Pre-CCTA nitrate use	4,563 (9.5%)	55 (0.1%)	4,674 (10.9%)	108 (0.1%)	4,105 (21.0%)	40 (0.1%)
Pre-CCTA aspirin use	6,533 (13.5%)	293 (0.3%)	13,404 (31.3%)	445 (0.5%)	7,621 (38.9%)	186 (0.5%)
Pre-CCTA cholesterol-lowering drug use	2,863 (5.9%)	260 (0.3%)	21,558 (50.4%)	393 (0.5%)	8,337 (42.6%)	172 (0.4%)
Pre-CCTA βblocker use	6,086 (12.6%)	235 (0.2%)	13,935 (32.6%)	294 (0.3%)	5,730 (29.3%)	137 (0.4%)
Pre-CCTA calcium antagonist use	3,650 (7.6%)	302 (0.3%)	7,750 (18.1%)	398 (0.5%)	3,716 (19.0%)	183 (0.5%)
Pre-CCTA p2y12 inhibitor use	181 (0.4%)	55 (0.1%)	2,129 (5.0%)	72 (0.1%)	741 (3.8%)	32 (0.1%)
Pre-CCTA direct oral anticoagulant use	149 (0.3%)	58 (0.1%)	3,521 (8.2%)	85 (0.1%)	483 (2.5%)	40 (0.1%)
Pre-CCTA vitamin K anticoagulant use	199 (0.4%)	43 (0.0%)	6,610 (15.4%)	95 (0.1%)	1,151 (5.9%)	45 (0.1%)
Nitrate use 0−180 d after CCTA	498 (1.0%)	92 (0.1%)	2,116 (4.9%)	148 (0.2%)	4,509 (23.0%)	69 (0.2%)
Aspirin use 0−180 d after CCTA	0	283 (0.3%)	19,212 (44.9%)	506 (0.6%)	12,674 (64.8%)	228 (0.6%)
Cholesterol-lowering drug use 0−180 d after CCTA	0	324 (0.3%)	31,113 (72.7%)	534 (0.6%)	14,497 (74.1%)	265 (0.7%)
βblocker use 0−180 d after CCTA	4,893 (10.1%)	306 (0.3%)	14,302 (33.4%)	403 (0.5%)	8,704 (44.5%)	203 (0.5%)
Calcium antagonist use 0−180 d after CCTA	3,636 (7.5%)	326 (0.3%)	8,389 (19.6%)	511 (0.6%)	5,118 (26.2%)	220 (0.6%)
p2y12 inhibitor use 0−180 d after CCTA	0	80 (0.1%)	3,191 (7.5%)	125 (0.1%)	5,459 (27.9%)	56 (0.1%)
Direct oral anticoagulant use 0−180 d after CCTA	0	83 (0.1%)	3,623 (8.5%)	107 (0.1%)	676 (3.5%)	57 (0.1%)
Vitamin K anticoagulant use 0−180 d after CCTA	0	71 (0.1%)	7,614 (17.8%)	135 (0.2%)	1,490 (7.6%)	74 (0.2%)

Patient Groups 1 to 3 refer to: (1) no post-CCTA preventive pharmacotherapy use (cholesterol-lowering drugs, antiplatelets or anticoagulants); (2) post-CCTA preventive pharmacotherapy use; and (3) revascularization or MI within 180 days post-CCTA. Controls are derived from the background population matched on age, gender and calendar year.

CCTA = coronary computed tomography angiography; n = number.

were diagnosed with MI or revascularized during the first 180 days after CCTA, had significantly higher ischemic event risks in comparison to their respective controls (Figures 1 to 2, Supplementary Table 3). The corresponding standardized relative risks of all clinical outcomes are shown in Figure 2.

Discussion

This large nationwide register-based study of 110,599 patients with first-time CCTA examinations from 2007 to 2017 and age-matched and gender-matched population controls examined long-term mortality and ischemic event risks in relation to preventive pharmacotherapy use within 180 days after CCTA and the occurrence of incident MI or revascularization during the first 180 days post-CCTA. Five-year mortality in CCTA-examined patients was significantly lower relative to population controls. Five-year MI or revascularization events were similarly lower for CCTA-examined patients except for those who were diagnosed with MI or revascularized within the first 180 days post-CCTA.

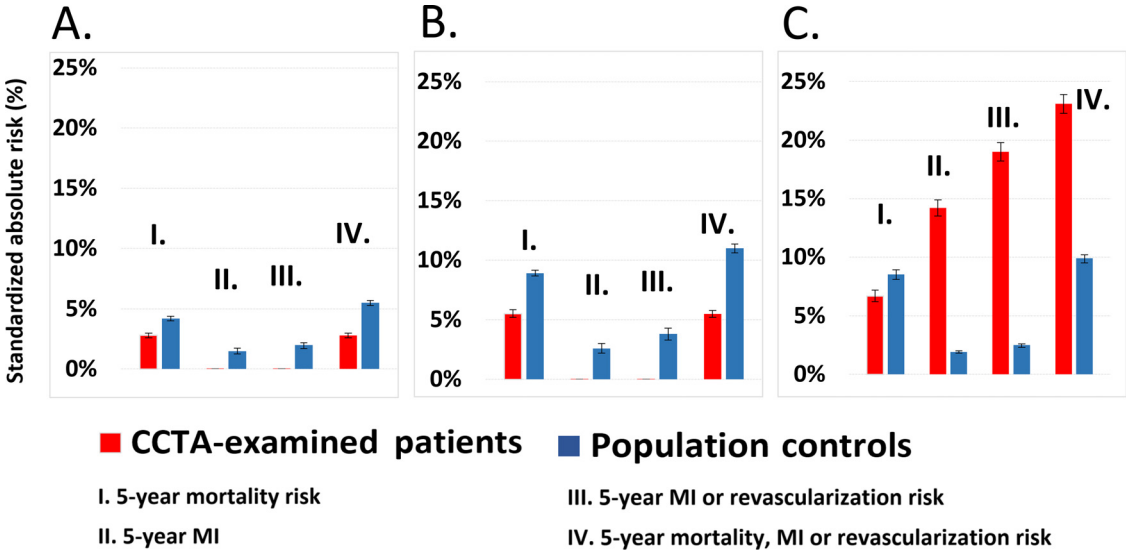

Figure 1. Patient Groups 1 to 3A-C refer to: (*A*) no post-CCTA preventive pharmacotherapy use (cholesterol-lowering drugs, antiplatelets or anticoagulants); (*B*) post-CCTA preventive pharmacotherapy use; and (*C*) revascularization or MI within 180 days post-CCTA. Controls are derived from the background population matched on age, gender, and calendar year. Multivariable Cox regression was used to obtain absolute risks of the outcomes standardized to the age, gender, selected co-morbidity and pharmacotherapy distributions of both CCTA-examined patients and the respective controls. The following covariates were included in the models: age, gender, hypertension, diabetes mellitus, chronic kidney disease, atrial fibrillation or flutter, heart failure, chronic obstructive pulmonary disease, nitrate, β-blocker, and calcium antagonist use. CCTA = coronary computed tomography angiography; MI = myocardial infarction.

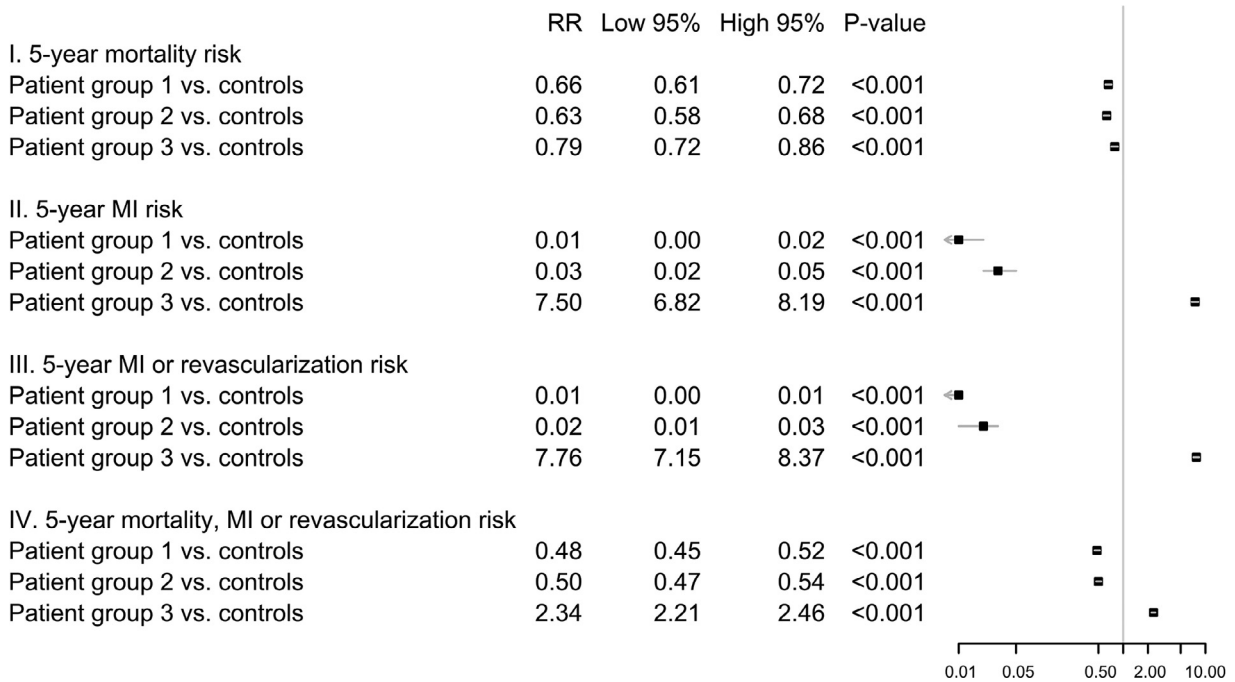

Figure 2. Patient Groups 1 to 3 refer to: (1) no post-CCTA preventive pharmacotherapy use (cholesterol-lowering drugs, antiplatelets, or anticoagulants); (2) post-CCTA preventive pharmacotherapy use; and (3) revascularization or MI within 180 days post-CCTA. Controls are derived from the background population matched on age, gender, and calendar year. Multivariable Cox regression was used to obtain relative risks of the outcomes standardized to the age, gender, selected co-morbidity and pharmacotherapy distributions of both CCTA-examined patients and the respective controls. The following covariates were included in the models: age, gender, hypertension, diabetes mellitus, chronic kidney disease, atrial fibrillation or flutter, heart failure, chronic obstructive pulmonary disease, nitrate, β-blocker, and calcium antagonist use. CCTA = coronary computed tomography angiography; RR = relative risk; Low/High 95% = lower and upper limit of 95% confidence interval; MI = myocardial infarction.

A number of studies have shown CCTA to be a valuable tool for the accuracy of CAD detection and prognosis. The prognostic discrimination provided by CCTA in patients with nonobstructive CAD has been found superior to standard functional testing.[1,2,21–24] Both Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) and SCOT-HEART demonstrated the superior ability of CCTA to inform clinical outcomes when compared with conventional functional testing.[1,2,25]

The present study adds to the current literature by demonstrating the prognostic value of different CCTA-examined populations based on post-CCTA preventive medical therapy or the occurrence of MI or revascularization on subsequent 5-year clinical outcomes in comparison to age-matched and gender-matched population controls. Interestingly, 5-year mortality outcomes were significantly lower for all CCTA-examined patient groups when compared with their respective controls. Presumed CV death was similarly significantly lower for groups 1 and 2 relative to their respective controls, whereas the difference was insignificant between group 3 and their respective controls. In addition, 5-year MI or revascularization events were similarly lower for CCTA-examined patients except for the CCTA-examined population who were diagnosed with MI or revascularized within the first 180 days post-CCTA. For this latter patient group, the ischemic event risk within the next 5 years remained elevated, whereas the risk of subsequent ischemic events for CCTA-examined patients without any of these events in the first 180 days was extremely low at <0.1%. As such, the clinical implication of our study is that the long-term ischemic event risk can be considered very low for CCTA-examined patients without MI or revascularization events within 180 days post-CCTA. This information is useful in the setting of a clinical complaint of chest pain after 180 days post-CCTA and within the next subsequent 5 years. Conversely, CCTA-examined patients with MI or revascularization events within 180 days post-CCTA have significantly elevated 5-year MI or revascularization risk.

We cannot rule out a healthy cohort bias, as CCTA-examined patients may constitute patients who more often seek medical attention for complaints and who may lead more healthy lives than controls of similar age and gender. Nonetheless, we observed an overweight of clinical risk factors related to CAD in CCTA-examined patients relative to age-matched and gender-matched population controls. The low long-term risk in CCTA-examined patients may be related to relevant early preventive medical therapy in risk patients. In further support of this notion, patients diagnosed with CAD by CCTA may have more efficient adherence to preventive medicine and other risk factor modifications than controls.[26]

In general, the observational design does not allow any conclusions regarding causality to be made, and the findings may not be generalized to other health care systems. However, the nationwide design, including a large all-comer cohort of CCTA-examined patients, minimizes selection bias based on geographical and demographical factors. A number of important clinical variables were unavailable, including the result of the CCTA, calcium score or angiogram data, symptoms before and after the CCTA test,

smoking history and family history of ischemic heart disease, and long-term drug adherence data. Although aspirin can be purchased over-the-counter, the clinical practice in Denmark is that patients are prescribed the drug when indicated after a CCTA, ensuring that its use will be captured by our registry-based methods. The lack of angiographic results of the CCTAs in this study also forced us to use a landmark approach, only including patients alive 180 days post-CCTA in the main analysis. This approach, however, allowed us to define distinct risk categories, with patients in group 1 most likely not having any significant CAD as secondary prevention medication was not prescribed within 180 days post-CCTA (the low-risk group). In contrast, patients in group 2 (moderate to higher risk) and group 3 (high to very high risk) were classified as having significant CAD with an indication for secondary preventive medication use, and group 3 patients were, in addition, diagnosed with MI or revascularized within 180 days post-CCTA. Lastly, and in vast contrast to the included number of 110,599 patients in the study population, only 761 patients who died during the first 180 days post-CCTA were excluded, justifying the landmark approach.

In conclusion, in this large nationwide register-based study of 110,599 patients who underwent first-time CCTA testing, the long-term cardiovascular risk can be considered very low, with MI or revascularization risks of <0.1%, if CCTA-examined patients are not diagnosed with MI or revascularized within 180 days post-CCTA. This information can be of use in the setting of a clinical complaint of chest pain after 180 days post-CCTA and within the next subsequent 5 years. In contrast, CCTA-examined patients with MI or revascularization events within 180 days post-CCTA continue to have a significantly elevated long-term ischemic event risk.

Disclosures

K. Kragholm: Speaker's honoraria from Novartis. P. Sogaard: Speaker for GE Healthcare, advisory board member (Novartis Pharmaceuticals Corp., Astra Zeneca Pharmaceuticals, Biotronik), research grants Wics, Bayer, and GE Healthcare. T. Zaremba: speaker's fee from AstraZeneca. C. Byrne: Speaker's honoraria from Bayer. L. Kober: Speakers honorarium from Novo, Novartis AstraZeneca and Boehringer. These disclosures are unrelated to the topic of the current manuscript and have not influenced the design and conduct of the study, nor in the collection, analysis, and interpretation of the data, and finally, not in the preparation, review, or submission of the manuscript. All other authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.04.035.

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