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ORIGINAL INVESTIGATIONS

Functional Testing or Coronary Computed Tomography Angiography in Patients With Stable Coronary Artery Disease

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ABSTRACT

BACKGROUND The choice of either anatomical or functional noninvasive testing to evaluate suspected coronary artery disease might affect subsequent clinical management and outcomes.

OBJECTIVES This study analyzed the association of initial noninvasive cardiac testing in outpatients with stable symptoms, with subsequent use of medications, invasive procedures, and clinical outcomes.

METHODS We studied patients enrolled in a Danish nationwide register who underwent initial noninvasive cardiac testing with either coronary computed tomography angiography (CTA) or functional testing (exercise electrocardiography or nuclear stress testing) from 2009 to 2015. Further use of noninvasive testing, invasive procedures, medications, and medical costs within 120 days were evaluated. Risks of long-term mortality and myocardial infarction (MI) were analyzed using adjusted Cox proportional hazard models.

RESULTS A total of 86,705 patients underwent either functional testing (n = 53,744, mean age 57.4 years, 49% males) or coronary CTA (n = 32,961, mean age 57.4 years, 45% males), and were followed for a median of 3.6 years. Compared with functional testing, there was significantly higher use of statins (15.9% vs. 9.1%), aspirin (12.7% vs. 8.5%), invasive coronary angiography (14.7% vs. 10.1%), and percutaneous coronary intervention (3.8% vs. 2.1%); all $p < 0.001$ after coronary CTA. The mean costs of subsequent testing, invasive procedures, and medications were higher after coronary CTA ($995 vs. $718; $p < 0.001$). Unadjusted rates of mortality (2.1% vs. 4.0%) and MI hospitalization (0.8% vs. 1.5%) were lower after coronary CTA than functional testing (both $p < 0.001$). After adjustment, coronary CTA was associated with a comparable all-cause mortality (hazard ratio: 0.96; 95% confidence interval: 0.88 to 1.05), and a lower risk of MI (hazard ratio: 0.71; 95% confidence interval: 0.61 to 0.82).

CONCLUSIONS In stable patients undergoing initial evaluation for suspected coronary artery disease, coronary CTA was associated with greater use of statins, aspirin, and invasive procedures, and higher costs than functional testing. Coronary CTA was associated with a lower risk of MI, but a similar risk of all-cause mortality.
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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

cath = invasive coronary angiography

CI = confidence interval

CTA = computed tomography angiography

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

In patients with symptoms suggestive of coronary artery disease (CAD), noninvasive cardiac testing is the initial step in establishing a diagnosis and guiding further management; yet, the preferred choice of noninvasive test remains uncertain. Most patients with a low to intermediate pre-test probability of CAD undergo a functional test, with exercise electrocardiography or nuclear stress testing, or an anatomical test, with coronary computed tomography angiography (CTA) (1). As the comparative effectiveness of these test options is not well established, the choice of initial testing strategy is affected by physician preference and test availability (2).

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Numerous studies have evaluated diagnostic certainty and short-term surrogate endpoints associated with initial noninvasive testing (3,4); however, hard endpoints have been less frequently evaluated. An initial strategy of coronary CTA may lead to increased use of further testing and revascularization, and greater costs than functional testing, which may or may not be associated with improved clinical outcomes (5). Recent large-scale randomized trials have suggested that there was little if any difference in long-term outcomes after coronary CTA compared with functional testing, but event rates were low (6,7). An observational study of Medicare beneficiaries showed higher costs after coronary CTA compared with functional testing, with no significant difference in all-cause mortality, but the follow-up was limited to 180 days (8). As these prior studies have demonstrated that the choice of initial testing does affect subsequent patient management, the question remains whether differences in testing strategy and subsequent treatment translate into differences in cardiac events and long-term survival.

In the present study, we used a contemporary nationwide cohort of stable patients undergoing initial noninvasive testing for CAD, with comprehensive follow-up. We hypothesized that the choice between functional and anatomical noninvasive cardiac testing would lead to differences in subsequent patient management and also affect long-term outcomes.

METHODS

DATA SOURCES. The single-payer health care system in Denmark provides equal access to free health care for all citizens, regardless of social and demographic characteristics. All health care services are recorded at the individual level using a unique personal identifier that enables linkage of administrative registries. The unique personal identifier assigned to all permanent residents ensures near-complete follow-up (99.8% in this study).

For the present study, we retrieved deidentified, linked data from a number of sources, including the National Patient Registry, which holds information on all hospital diagnoses (including outpatient clinic), tests, and procedures performed in Denmark since 1977, coded according to the International Classification of Disease-Version 10; and the Registry for Medicinal Product Statistics, which holds information on all prescriptions filled at a Danish pharmacy since 1995, coded according to the Anatomical Therapeutic Classification system (9). Hospitals are reimbursed on a fee-for-service basis, and patients are partially reimbursed when filling prescriptions, which ensures high accuracy for registration of hospital diagnoses and outpatient filled prescriptions (10,11). We retrieved sex and dates of birth and death from the National Population Registry, and the date and cause of death from the National Cause of Death Registry. The study was approved by the Danish Data Protection Agency (GEH-2014-014, I-Suite nr: 02732). According to Danish law, investigators using deidentified data are not required to obtain individual informed consent, approval by institutional review boards, or approval by an ethical committee.

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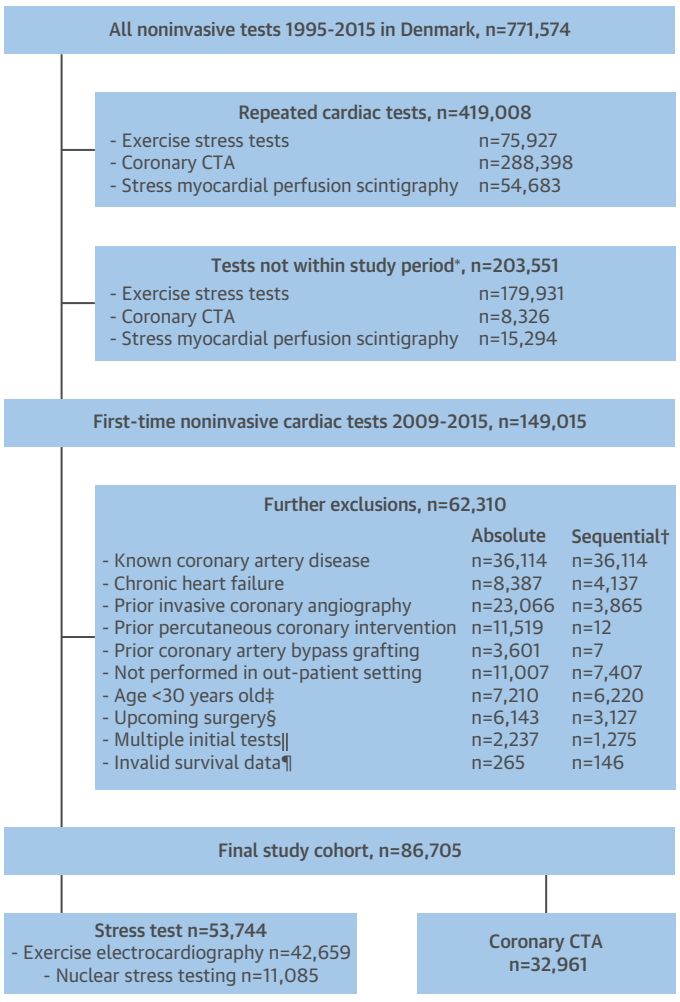
STUDY POPULATION. Functional testing included exercise electrocardiography and nuclear stress testing. Noninvasive anatomical assessment was performed by coronary CTA. Stress echocardiography and cardiovascular magnetic resonance imaging is not routinely used for diagnosing CAD in Denmark. The conduct and interpretation of exercise electrocardiography is guided by national recommendations and performed during exercise on a stationary bike (12). Nuclear stress testing was performed during physical exercise (24%) or pharmacological stress (76%), using single-photon emission computed tomography, which is standard for nuclear stress testing in Denmark (13). For coronary CTA, national recommendations have been available to guide both conduct and interpretation since 2010 (14).

Figure 1 outlines the selection of the study population, and Online Table 1 summarizes coding for tests, procedures, pharmacotherapy, and comorbidities. We identified all initial noninvasive cardiac tests performed in an outpatient clinical setting in Denmark between January 1, 2009, and August 31, 2015, and followed all patients until December 31, 2015. Thus, patients undergoing initial testing during hospitalization due to suspected unstable angina or myocardial infarction (MI) were excluded. None of the relevant tests are routinely performed in an emergency room setting in Denmark. The last inclusion date for this study was chosen to allow for a minimum follow-up of 120 days. We excluded patients with a prior diagnosis of either CAD or heart failure, or any history of invasive coronary angiography (cath), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). We also excluded patients <30 years of age (in whom cardiac testing was most likely performed for other indications than suspected CAD), patients with noncardiac surgery within 30 days (in whom cardiac testing may have been performed for pre-operative evaluation), tests performed during hospital admission (as these may have been related to a cardiac event), and patients who had >1 noninvasive cardiac test on the same day (because of ambiguity regarding study exposure). Complete records on tests and procedures were available since 1995, and records on prior diagnosis were available since 1977, which allowed for thorough application of the exclusion criteria, as patients with a noninvasive test or exclusion diagnosis prior to the beginning of our study period on January 1, 2009, would have been excluded.

STUDY VARIABLES. Baseline use of pharmacotherapy was defined as a prescription filled within the 120 days prior to initial testing. This interval was chosen to allow for patients to deplete their stock and refill a prescription, as pack size is most often ≤100 tablets (coding details available in Online Table 1).

Prior comorbidities were defined from primary or secondary diagnoses upon hospital discharge (positive predictive values ranging from 96% to 100%) (10), with the exception of heart failure, which was defined as a diagnosis or use of loop diuretics, as previously described (10,15) (coding details available in Online Table 1).

FIGURE 1 Flowchart



*We included tests performed between January 1, 2009, and August 31, 2015. Complete records of noninvasive tests were available since 1995, but coronary computed tomography angiography (CTA) was not used regularly in clinical practice until 2009. †Number of patients excluded step-by-step in the order of the variables listed. ‡These tests may have been performed for indications other than suspected CAD (i.e., elite athlete testing). §If any type of surgery was performed within 30 days following initial testing, we excluded the patient assuming that the test was part of pre-operative evaluation rather than evaluation for CAD. ‖Patients tested with >1 noninvasive cardiac test on the first day were excluded due to study exposure ambiguity. ¶A small number of patients could not be accounted for as alive, dead, or emigrated in our registries.

TABLE 1 Patient Characteristics

	Functional Testing (n = 53,744)	Coronary CTA (n = 32,961)	p Value	Standardized Differences*
Demographics				
Age, yrs	57.4 ± 12.8	57.4 ± 10.9	0.54	0.004
Male	26,227 (48.8)	14,822 (45.0)	<0.001	0.077
Prior echocardiography	23,464 (43.7)	19,104 (58.0)	<0.001	0.289
Tests per year				
2009	11,410 (21.2)	2,299 (7.0)	<0.001	0.418
2010	10,113 (18.8)	3,114 (9.4)	<0.001	0.271
2011	8,407 (15.6)	4,576 (13.9)	<0.001	0.050
2012	7,961 (14.8)	5,315 (16.1)	<0.001	0.036
2013	6,647 (12.4)	5,661 (17.2)	<0.001	0.136
2014	5,723 (10.6)	6,336 (19.2)	<0.001	0.242
2015 (January to August)†	3,483 (6.5)	5,660 (17.2)	<0.001	0.336
Medications				
Statin	12,498 (23.3)	8,965 (27.2)	<0.001	0.091
Renin-angiotensin system inhibitor	13,480 (25.1)	8,331 (25.3)	0.52	0.039
Glucose lowering	3,945 (7.3)	2,009 (6.1)	<0.001	0.004
Digoxin	639 (1.2)	231 (0.7)	<0.001	0.059
Thiazide	5,235 (9.7)	2,661 (8.1)	<0.001	0.035
Spironolactone	513 (1.0)	354 (1.1)	0.09	0.012
Beta blocker	8,722 (16.2)	5,830 (17.7)	<0.001	0.050
Calcium antagonist	7,839 (14.6)	4,411 (13.4)	<0.001	0.005
Nitrate: long acting	242 (0.5)	138 (0.4)	0.49	0.075
Nitrate: short acting	5,060 (9.4)	3,858 (11.7)	<0.001	0.050
Aspirin	10,444 (19.4)	8,217 (24.9)	<0.001	0.133
Dipyridamole	860 (1.6)	433 (1.3)	0.001	0.024
Clopidogrel	1,002 (1.9)	688 (2.1)	0.02	0.016
Vitamin K antagonists	2,058 (3.8)	994 (3.0)	<0.001	0.045
Comorbidities				
Diabetes with complications	1,858 (3.5)	885 (2.7)	<0.001	0.045
Atrial fibrillation	3,680 (6.8)	1,731 (5.3)	<0.001	0.067
Chronic lung disease	2,080 (3.9)	1,150 (3.5)	0.004	0.020
Peripheral vascular disease	689 (1.3)	374 (1.1)	0.06	0.013
Cerebrovascular disease	2,455 (4.6)	1,419 (4.3)	0.07	0.013
Venous thromboembolism	1,387 (2.6)	713 (2.2)	<0.001	0.027
Anemia	1,451 (2.7)	823 (2.5)	0.07	0.013
Coagulation deficiencies	1,269 (2.4)	721 (2.2)	0.10	0.012
Cancer	3,888 (7.2)	2,261 (6.9)	0.04	0.015
Cancer: metastatic	376 (0.7)	197 (0.6)	0.07	0.013
Liver disease	823 (1.5)	516 (1.6)	0.69	0.003
Renal disease	961 (1.8)	238 (0.7)	<0.001	0.096
Rheumatological disease	2,326 (4.3)	1,710 (5.2)	<0.001	0.040

Values are mean ± SD or n (%). Demographics, medication use, and prior comorbidities stratified by choice of initial noninvasive test. *Standardized differences <0.10 indicates minimal differences between groups. †2015 does not represent a full year, as patients tested after August 31, 2015, were not included to allow for a minimum follow-up of 120 days.

CTA = computed tomography angiography.

We estimated mean costs of downstream noninvasive testing, cath, revascularization, and medication within 120 days from the initial test for each patient, based on both Danish and U.S. cost weights (Online Table 2) (16-18). Long-term costs related to procedural complications, medications, treatment of restenosis, and any follow-up events were not assessed.

SHORT- AND LONG-TERM OUTCOMES. Changes in drug use within the 120 days following initial testing were defined by both pre- and post-test filled prescriptions within a before and after 120-day window as continued, discontinued, initiated, or no therapy. Within the 120 days following index testing we assessed the use of further noninvasive testing with exercise electrocardiography, nuclear stress testing, or coronary CTA, as well as invasive procedures including cath, PCI, and CABG. The cutoff at 120 days was chosen based on a review of our data, which showed that most changes in management after initial testing were made within 120 days (Online Figures 1A to 1C).

The long-term primary endpoint was all-cause mortality, defined by vital status in the National Population Registry. The secondary endpoints were hospital-verified fatal and nonfatal MI during admission or emergency room visit, defined as a primary diagnosis of acute MI coded as I21 in the International Classification of Disease-Version 10, as well as the combined endpoint of all-cause mortality and MI.

STATISTICS. We used the chi-square test and Student *t* tests to examine differences in categorical and continuous variables between test groups, respectively, and the nonparametric Wilcoxon Mann-Whitney test to test for differences in costs. We used Cox proportional hazard regression models to estimate hazard ratios (HRs) with 95% confidence intervals (CIs), both unadjusted and adjusted for age, sex, calendar year, echocardiography prior to index testing, pharmacotherapy, and comorbidities, as listed in **Table 1**. We analyzed the probability of filling a prescription for statin, aspirin, renin-angiotensin system inhibitors, or beta-blockers within 120 days after the test. As these analyses were adjusted for drug use prior to index testing, results may be interpreted as predictors of drug initiation. We also estimated long-term risks of all-cause mortality, MI, and the combined endpoint associated with the initial noninvasive test. Patients undergoing functional testing served as reference in all models.

In a sensitivity analysis, we re-examined the primary and secondary endpoints using a weighted causal inference model as an alternative method to control for confounding (19). We estimated the inverse probability weights based on all variables in **Table 1**, using a generalized boosted model with up to 15,000 iterations and the mean Kolmogorov-Smirnov effect size as the preferred stopping rule. We report weighted baseline characteristics and weighted Cox proportional hazard regression models for analyses of long-term outcomes, without any further adjustment.

TABLE 2 Drug Use Within 120 Days

		Medication Use Before and After Testing*				Proportion Having Medication Changed†	
		Initiated	Continued	Discontinued	None		p Value‡
Statins	Coronary CTA	15.9	21.8	5.4	56.9	21.3	
	Functional testing	9.1	19.0	4.3	67.7	13.4	<0.001
Aspirin	Coronary CTA	12.7	12.7	12.2	62.3	24.9	
	Functional testing	8.5	11.9	7.5	72.1	16.0	<0.001
Renin-angiotensin system inhibitor	Coronary CTA	3.9	22.6	2.7	70.8	6.6	
	Functional testing	4.3	22.0	3.0	70.7	7.3	<0.001
Beta blocker	Coronary CTA	6.5	12.8	4.9	75.8	11.4	
	Functional testing	7.9	12.7	3.5	75.9	11.4	0.88
Calcium antagonist	Coronary CTA	4.6	10.6	2.8	82.1	7.4	
	Functional testing	4.3	11.5	3.1	81.1	7.4	0.59
Nitrates: short acting	Coronary CTA	3.2	0.7	11.0	85.1	14.2	
	Functional testing	3.0	0.7	8.8	87.6	11.8	<0.001
Thiazide	Coronary CTA	2.2	5.8	2.2	89.8	4.4	
	Functional testing	2.8	6.8	2.9	87.5	5.7	<0.001
Aldosterone antagonist	Coronary CTA	0.5	0.8	0.2	98.5	0.7	
	Functional testing	0.4	0.7	0.3	98.7	0.7	0.21
Dipyridamole	Coronary CTA	0.1	1.1	0.3	98.6	0.4	
	Functional testing	0.1	1.3	0.3	98.3	0.4	0.01
Clopidogrel	Coronary CTA	4.3	1.6	0.5	93.7	4.8	
	Functional testing	2.5	1.5	0.3	95.6	2.8	<0.001

Values are %. Patients undergoing initial testing may initiate, continue, discontinue, or remain untreated within 120 days. Estimates for the sum of patients changing therapy (initiate or discontinue) are shown. All estimates in this table are unadjusted; adjusted probabilities of initiating therapy are available in Online Table 3. *Defined as claimed prescriptions in a "before period" within 120 days prior to testing and again for an "after period" within 120 days after the test. Initiated: patients did not claim a prescription in the before period, but did in the after period. Continued: patients claimed a prescription in the before period and the after period. Discontinued: patients claimed a prescription in the before period but not the after period. None: patients did not claim a prescription either in the before or after period. †Medication change defined as sum of patients initiating or discontinuing therapy. ‡The p value for the difference in proportions having medication changed.

CTA = computed tomography angiography.

Diagnostic graphs for the treatment weight estimation process are shown in Online Figures 2A to 2C.

We used SAS version 9.4 (SAS Institute, Cary, North Carolina) for most analyses, and the R statistical software version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) for estimating treatment weights and for graphical illustrations. We considered a 2-sided p value of < 0.05 to be statistically significant.

RESULTS

BASELINE CHARACTERISTICS. Over 770,000 noninvasive cardiac tests were performed in Denmark between 1995 and 2015, with 149,015 initial tests performed between 2009 and 2015 (**Figure 1**). After excluding patients with established cardiovascular disease, the final study cohort consisted of 86,705 patients, divided into a functional testing group that underwent exercise electrocardiography (n = 42,659) or nuclear stress testing (n = 11,085), and an anatomical testing group that underwent coronary CTA (n = 32,961). Mean age was the same in the 2 testing groups (57.4 years), but the coronary CTA group was less frequently male (45% vs. 49% male; $p < 0.001$) (**Table 1**). The annual rate of initial noninvasive functional or anatomical testing declined by 12% between 2009 (n = 13,709 tests) and 2014 (n = 12,059 tests), with a shift in use from functional testing (n = 11,410 to 5,723) to coronary CTA (n = 2,299 to 6,336) over time. Use of drugs at baseline was slightly higher in the coronary CTA testing group compared with the functional testing group. Patients in the functional testing group generally had more comorbidities than patients in the coronary CTA group (**Table 1**).

DRUG USE FOLLOWING INITIAL TESTING. Statin therapy was more frequently changed (initiated or discontinued) in the coronary CTA group than in the functional testing group (21.3% vs. 13.4%, respectively; $p < 0.001$). Also, aspirin therapy was more often changed in the coronary CTA group than in the functional testing group (24.9% vs. 16.0%, respectively; $p < 0.001$) (**Table 2**). After adjustment for differences at baseline, coronary CTA was significantly associated with initiation of statins (HR: 1.42; 95% CI: 1.39 to 1.46) and aspirin (HR: 1.36; 95% CI: 1.32 to 1.40)

TABLE 3 Downstream Testing, Revascularization, and Costs Within 120 Days

	Functional Testing Group (n = 53,744)	Coronary CTA Group (n = 32,961)	p Value	Standardized Differences*
Further testing (individual)				
Exercise electrocardiography	1,117 (2.1)	941 (2.9)	<0.001	0.050
Coronary CTA	3,522 (6.6)	424 (1.3)	<0.001	0.274
Nuclear stress testing	2,588 (4.8)	1,345 (4.1)	<0.001	0.036
Cath	5,427 (10.1)	4,855 (14.7)	<0.001	0.141
Further testing (combinations)				
No further testing	42,662 (79.4)	26,165 (79.4)	0.99	0.000
Noninvasive only	5,655 (10.5)	1,941 (5.9)	<0.001	0.169
Cath only	4,292 (8.0)	4,265 (12.9)	<0.001	0.162
Noninvasive + cath	1,135 (2.1)	590 (1.8)	0.001	0.023
Invasive procedures				
No invasive procedure	48,285 (89.8)	28,033 (85.0)	<0.001	0.145
Cath only	3,767 (7.0)	3,248 (9.9)	<0.001	0.103
PCI	1,167 (2.2)	1,241 (3.8)	<0.001	0.094
CABG	525 (1.0)	439 (1.3)	<0.001	0.033
Cath followed by revascularization†	(30.6)	(33.1)	0.006	0.054
Costs in U.S. dollars‡				
Danish costs	718 ± 3,605	995 ± 4,250	<0.001	0.071
U.S. costs	1,006 ± 4,172	1,408 ± 4,978	<0.001	0.090

Values are n (%) or mean ± SD. Further testing within 120 days is shown as individual components and as combinations of tests. Revascularization procedures assume preceding cath. All numbers do not summarize as intended due to a small number of patients having >1 repeat noninvasive test or having cath, PCI, and CABG within 120 days. Also, a very small number of patients underwent PCI or CABG without a prior record of cath. *Standardized difference < 0.10 indicates minimal differences between groups. †Calculated as the sum of PCI and CABG over the sum of cath, PCI, and CABG as an indicator of appropriate/inappropriate use of invasive testing. ‡Costs include further noninvasive testing, cath, revascularization, and use of statin and aspirin within 120 days. Details are available in Online Table 2.

CABG = coronary artery bypass grafting; Cath = invasive coronary angiography; CTA = computed tomography angiography; PCI = percutaneous coronary intervention.

(Online Table 3). Furthermore, patients in the coronary CTA group were more likely to be switched from a regular statin (e.g., simvastatin) to a potent statin (e.g., atorvastatin) (1.9% vs. 0.8%, respectively; p < 0.001) (Online Table 4). Initiation of statin and aspirin was also significantly associated with older age, male sex, and prior therapy with glucose-lowering drugs (all p < 0.001) (Online Table 3).

ADDITIONAL TESTING AND REVASCULARIZATION. The majority of patients (79%) did not undergo further testing within the 120 days following initial testing. Downstream noninvasive testing was performed less often following coronary CTA than after functional testing (5.9% vs. 10.5%; p < 0.001), whereas cath was performed more often following coronary CTA (12.9% vs. 8.0%; p < 0.001). Coronary revascularization was significantly more common in the coronary CTA group than the functional testing group, both with PCI (3.8% vs. 2.2%; p < 0.001) and with CABG (1.3% vs. 1.0%; p < 0.001). Coronary revascularization was more frequently performed in patients referred to cath after coronary CTA than cath after functional testing (33.1% vs. 30.6%; p < 0.001) (**Table 3**).

Using Danish cost weights, the costs of downstream tests, revascularization, statin, and aspirin use within 120 days was significantly higher in the coronary CTA group ($995 vs. $718; p < 0.001) (**Table 3**). Costs were also higher when measured using U.S. cost weights, and when the cost of initial testing was included (Online Table 2).

LONG-TERM RISKS OF MORTALITY AND MI. Over a median follow-up of 3.6 years (interquartile range 2.0 to 5.3 years; range 0.0 to 7.0 years), 2.1% of the coronary CTA group and 4.0% of the functional testing group died of any cause (p < 0.001) (Online Figure 3A). Rates of MI were significantly lower in the coronary CTA group than in the functional testing group (0.8% vs. 1.5%; p < 0.001) (Online Figure 3B). After adjusting for differences at baseline, risks of all-cause mortality were similar in the coronary CTA compared with the functional testing group (HR: 0.96; 95% CI: 0.88 to 1.05). The adjusted risk of MI was significantly lower in the coronary CTA group (HR: 0.71; 95% CI: 0.61 to 0.82) compared with the functional testing group (**Central Illustration**).

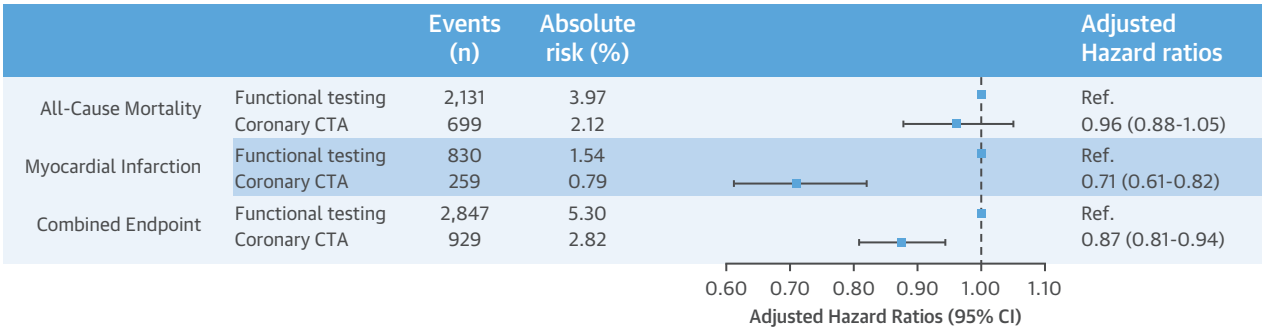
In sensitivity analyses, we compared the coronary CTA group with the exercise ECG group and single-photon emission computed tomography group individually. In the coronary CTA group there was no difference in the risk of all-cause mortality compared with the exercise ECG group (HR: 1.03; 95% CI: 0.93 to 1.14), whereas risks were significantly lower compared with the single-photon emission tomography group (HR: 0.78; 95% CI: 0.69 to 0.88). Risks of MI in the coronary CTA group were significantly lower compared with the exercise ECG group (HR: 0.72; 95% CI: 0.61 to 0.84) and the single-photon emission tomography group (HR: 0.66; 95% CI: 0.54 to 0.80).

WEIGHTED CAUSAL INFERENCE ANALYSES. Weighted baseline characteristics were well balanced for all variables (Online Table 5). In the weighted analysis, coronary CTA was associated with lower risks of all-cause mortality (weighted HR: 0.88; 95% CI: 0.79 to 0.97). The risk of MI remained significantly lower in the coronary CTA group (weighted HR: 0.64; 95% CI: 0.54 to 0.76), as did the risk of the combined endpoint (weighted HR: 0.81; 95% CI: 0.74 to 0.88) (Online Figure 4).

DISCUSSION

In this nationwide cohort study of patients undergoing initial diagnostic evaluation for suspected stable CAD, patients undergoing coronary CTA were more likely to initiate treatment with a statins and aspirin, to undergo cath, and to undergo coronary revascularization

CENTRAL ILLUSTRATION **Long-Term Risks of All-Cause Mortality and MI**



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Median follow-up was 3.6 years (interquartile range: 2.0 to 5.3 years; range: 0.0 to 7.0 years). All analyses were adjusted for sex, age, calendar year, prior echocardiography, medications, and comorbidities listed in Table 1. Myocardial infarctions (MIs) included fatal and nonfatal events. The combined endpoint included all-cause mortality and myocardial infarction. Patients who had an MI and later died were censored at the time of the MI event. CI = confidence interval; CTA = computed tomography angiography.

than patients having initial functional testing. These differences in management led to 39% higher costs within 120 days in the coronary CTA group ($995 vs. $718). Rates of adverse events and death were low in this population; yet, over a median follow-up of 3.6 years, patients in the coronary CTA group had a 29% lower risk of MI, with a similar risk of all-cause mortality.

CHOICE OF INITIAL TESTING. The comparative effectiveness of functional versus anatomical testing for suspected CAD has become an important question with the recent increase in use of coronary CTA testing. Two large clinical trials have randomized symptomatic patients with suspected stable CAD to management guided either by coronary CTA or functional testing. The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial randomized 10,003 patients to coronary CTA or functional testing, primarily nuclear stress testing, and did not show a significant difference in the primary composite endpoint (all-cause mortality, myocardial infarction, unstable angina, and procedural complication) with 161 events versus 151 events ($p = 0.75$) over a median follow-up of 2 years (7). The SCOT-HEART (Scottish Computed Tomography of the Heart) trial randomized 4,146 patients to undergo coronary CTA in addition to standard of care testing, primarily exercise electrocardiography, and demonstrated that coronary CTA improved the diagnostic certainty (6). In the SCOT-HEART trial, the secondary endpoints, including both fatal and nonfatal MI, did not differ significantly, with 26 events versus 42 events ($p = 0.053$) in coronary CTA versus standard care over a median follow-up of 1.7 years (6). The present study included over 8× as many patients, followed them for a longer time (median 3.6 years), and provided a larger number of events (2,830 deaths and 1,089 MIs) than the PROMISE and SCOT-HEART trials. Consistent with the findings of these trials and a recent meta-analysis (20), we found no difference in mortality between the coronary CTA and the functional testing group. However, we did observe a 29% lower risk of MI in the coronary CTA group, which is consistent with the trends toward fewer MIs reported by the PROMISE and SCOT-HEART trials, and very similar to the 31% and 47% reduction in risk of MIs reported in 2 recent meta-analyses (20,21). Although our study was not randomized, we used several statistical methods to control for confounding, including multivariable regression models and an advanced causal inference method based on inverse probability weighting.

PATIENT MANAGEMENT FOLLOWING INITIAL TESTING. Initial evaluation of patients with suspected CAD changes subsequent clinical management. We found that patients were significantly more likely to change the use of several medications after coronary CTA, particularly statins and aspirin. These medication changes included both initiation and discontinuation, and it is likely that patients initiated medications because of an abnormal coronary CTA result and discontinued them because of a normal coronary CTA

result. These hypotheses are supported by findings from the SCOT-HEART trial, which showed that antiplatelet agents, statins, and antianginal medications were all more likely to be initiated after an abnormal coronary CTA, and were all more likely to be discontinued after a normal coronary CTA (22). Two prior observational studies in patients undergoing initial coronary CTA with available data on coronary CTA results and the extent of atherosclerosis found that statin treatment increased following coronary CTA, especially in patients with obstructive CAD (23,24). One study showed an increase in use of aspirin from 10% to 46% of patients with a coronary CTA showing no CAD (23), whereas the other study showed a decrease in treatment from 35% to 25% of patients with a coronary CTA showing no CAD (24). In this study, coronary CTA results were not available, but in patients undergoing later invasive testing or revascularization, 70% of patients with initial functional testing and 85% of patients with initial coronary CTA initiated, continued, or intensified treatment compared with 30% and 40%, respectively, in the entire study population (Online Table 4). Targeted and appropriate use of clinically effective preventive medications, such as statins and aspirin, after coronary CTA may have contributed to a later reduction in coronary events.

Patterns of subsequent testing also differed significantly between the functional testing and the coronary CTA group. Even though 79% of patients in each group did not undergo further downstream testing, patients in the coronary CTA group were significantly more likely to be referred to subsequent cath, whereas patients who had initial functional testing were significantly more likely to have another noninvasive test (most often coronary CTA) performed. The increased use of cath after coronary CTA has been reported consistently in several prior studies, including the PROMISE and SCOT-HEART trials (6,7,20).

ECONOMIC OUTCOMES. In this registry study, the greater use of cath and revascularization after coronary CTA led to significantly higher costs over 120 days of follow-up: 39% higher using Danish reimbursement rates and 40% higher using U.S. Medicare reimbursement rates. Increased costs were mainly due to more frequent use of cath and revascularization in the coronary CTA group, which has also been shown in the SCOT-HEART and PROMISE economic analyses (22,25). The PROMISE trial reported a trend toward higher costs with coronary CTA over 90 days ($2,494 vs. $2,240), and the SCOT-HEART trial found that coronary CTA led to 32% higher costs over 6 months ($1,900 vs. $1,438; $p < 0.001$). Also, coronary CTA led to significantly higher costs than functional testing in a large-scale U.S. Medicare population (8). It is plausible that these higher downstream costs are driven by greater use of expensive invasive procedures after coronary CTA. The question remains whether the higher costs of using coronary CTA as an initial test are justified by improved clinical outcomes. In this study we found lower rates of MI after initial coronary CTA in this study, which arguably could justify the higher costs. We have not, however, performed a formal cost-effectiveness evaluation of coronary CTA versus functional testing, which would require additional data on late costs and quality of life, and a formal model of the effects on long-term outcomes.

STUDY LIMITATIONS. This observational study has inherent limitations, primarily that the initial diagnostic test was selected by the treating clinician and not assigned randomly. Even though we used well-accepted statistical methods to control for differences in baseline characteristics in the coronary CTA and the functional testing groups, we cannot exclude the possibility of residual selection bias. Because the present study was based on health care registries, we lacked important clinical data, such as the type and severity of angina symptoms, as well as the indication for, and results of, the coronary CTAs, functional tests, and caths. Information on use of fractional flow reserve, intravascular ultrasound, and optical coherence tomography was not available. Some coronary CTAs may have been performed to evaluate congenital or valvular heart disease rather than suspected ischemic heart disease. However, excluding the 2.3% of patients with a diagnosis of valve disease prior to testing did not affect the results (data not shown). Information on adverse events during testing were unknown, but previous studies have found these to occur at low rates and be self-limiting (26). Although we were not able to calculate the formal pre-test probability of CAD due to unknown type of angina, we adjusted the analyses for a large number of baseline risk factors. Furthermore, as current guidelines clearly state that the small proportion of patients with a high pre-test probability should undergo initial cath, and patients with low pre-test probability should not be tested, the potential effect of this bias is likely to be small. As the initial noninvasive cardiac test itself is unlikely to have any direct effect on long-term prognosis, the difference in long-term risk of MI is most likely attributable to differences in downstream patient management.

The study design does not, however, allow us to identify the specific elements of patient management that contributed to differences in long-term outcomes. Finally, this study was based on medical practice in Denmark, which may differ from the practice patterns of other countries, but the similarity of several of our results to the results of studies done in the United States does suggest that our findings may be generalizable.

CONCLUSIONS

An initial strategy of coronary CTA to evaluate suspected stable CAD appears to be associated with greater use of preventive cardiac medications and invasive cardiac procedures, including coronary revascularization. The more intensive clinical management of patients after coronary CTA might ultimately lead to improved clinical outcomes, particularly reductions in acute coronary syndromes. The clinical effectiveness, and cost-effectiveness, of visualizing coronary anatomy noninvasively with coronary CTA, rather than performing functional testing, deserves further study.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In stable patients undergoing initial evaluation for suspected CAD, coronary CTA was associated with more frequent use of statins, aspirin, and invasive coronary procedures, and higher costs than functional testing. Patients undergoing coronary CTA faced a lower risk of subsequent MI but a similar risk of all-cause mortality compared with those evaluated by functional tests.

TRANSLATIONAL OUTLOOK: Further studies of the downstream consequences of initial noninvasive testing modalities for stable patients with suspected CAD are needed to appreciate the relative value of various diagnostic and management strategies.

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APPENDIX For supplemental tables and figures, please see the online version of this article.