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ORIGINAL INVESTIGATIONS

Impact of Plaque Burden Versus Stenosis on Ischemic Events in Patients With Coronary Atherosclerosis

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ABSTRACT

BACKGROUND Patients with obstructive coronary artery disease (CAD) are at high risk for cardiovascular disease (CVD) events. However, it remains unclear whether the high risk is due to high atherosclerotic disease burden or if presence of stenosis has independent predictive value.

OBJECTIVES The purpose of this study was to evaluate if obstructive CAD provides predictive value beyond its association with total calcified atherosclerotic plaque burden as assessed by coronary artery calcium (CAC).

METHODS Among 23,759 symptomatic patients from the Western Denmark Heart Registry who underwent diagnostic computed tomography angiography (CTA), we assessed the risk of major CVD (myocardial infarction, stroke, and all-cause death) stratified by CAC burden and number of vessels with obstructive disease.

RESULTS During a median follow-up of 4.3 years, 1,054 patients experienced a first major CVD event. The event rate increased stepwise with both higher CAC scores and number of vessels with obstructive disease (by CAC scores: 6.2 per 1,000 person-years (PY) for CAC = 0 to 42.3 per 1,000 PY for CAC >1,000; by number of vessels with obstructive disease: 6.1 per 1,000 PY for no CAD to 34.7 per 1,000 PY for 3-vessel disease). When stratified by 5 groups of CAC scores (0, 1 to 99, 100 to 399, 400 to 1,000, and >1,000), the presence of obstructive CAD was not associated with higher risk than presence of nonobstructive CAD.

CONCLUSIONS Plaque burden, not stenosis per se, is the main predictor of risk for CVD events and death. Thus, patients with a comparable calcified atherosclerosis burden generally carry a similar risk for CVD events regardless of whether they have nonobstructive or obstructive CAD. (J Am Coll Cardiol 2020;76:2803–13) © 2020 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium

CAD = coronary artery disease

CTA = computed tomography angiography

CVD = cardiovascular disease

MI = myocardial infarction

Coronary artery disease (CAD) has a long pre-clinical phase during which it develops slowly over the course of years or decades, before manifesting itself clinically due to diffuse nonobstructive disease, stenoses, or thrombosis (1,2). Patients with symptomatic obstructive CAD are known to be at high risk for subsequent major cardiovascular disease (CVD) events and are therefore recommended to receive lifelong secondary preventive treatments including statins and aspirin (3–5). However, it remains unknown whether the high risk provided by presence of obstructive CAD is due to stenosis per se, or due to its correlation with total atherosclerotic plaque burden.

The past decade has seen dramatic advances in computed tomography (CT) hardware and software with improved spatial and temporal resolution. The value of computed tomography angiography (CTA) has been established and endorsed by societal guidelines as the first-line diagnostic test for patients with suspected CAD (3,6). CTA provides detailed information on CAD severity, which ranges from no CAD, to nonobstructive CAD, and to multivessel obstructive CAD (7,8). It is generally assumed that patients with obstructive disease are at higher risk of subsequent CVD events than patients with nonobstructive disease. Thus, patients with obstructive disease are recommended to receive more aggressive secondary prevention therapies (9–11). However, there is evidence that risk of future events may not abruptly increase with the presence of stenosis. Rather, this risk may be shaped by the total burden of atherosclerotic disease (i.e., as assessed by coronary artery calcium [CAC] scores) (12).

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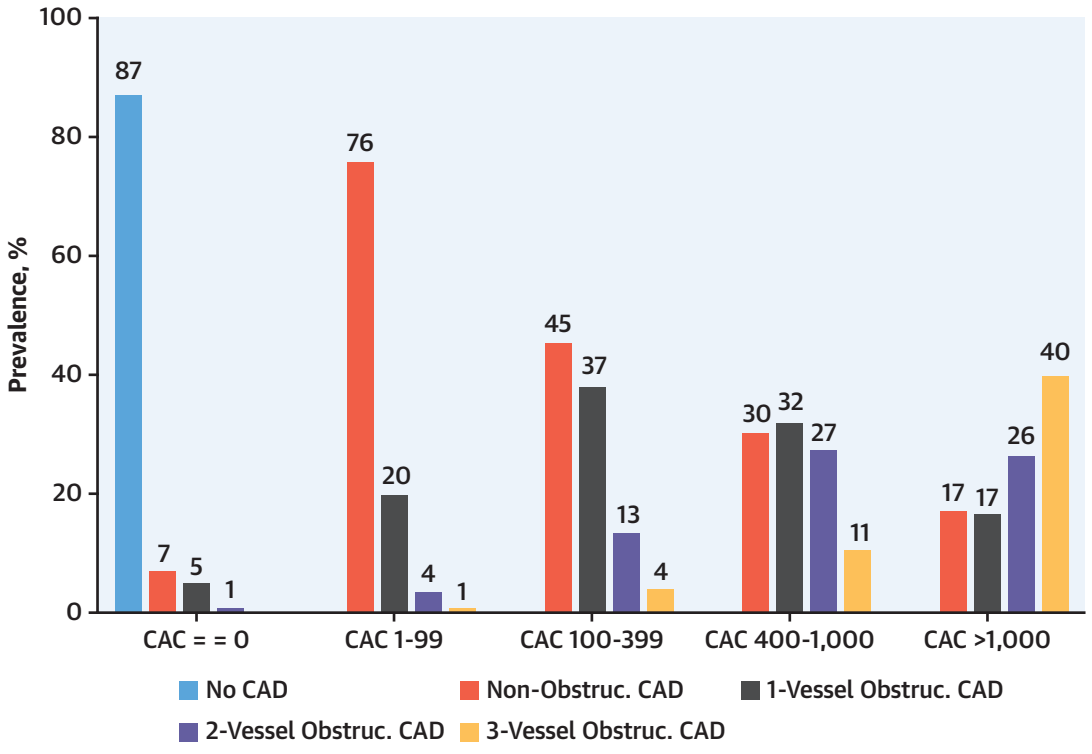
In the present study, we used data from the WDHR (Western Denmark Heart Registry) to evaluate if obstructive CAD carries independent risk beyond atherosclerotic disease burden (as measured by CAC scores) for subsequent specific CVD events (myocardial infarction [MI], stroke, and all-cause death). WDHR data provide a unique opportunity to address this issue, as they include CAC measurements and angiographic evaluation for all patients in the registry.

TABLE 1 Baseline Characteristics of Patients From the Western Denmark Heart Registry

	All (N = 23,759)	No or Nonobstructive Disease (n = 18,716)	Obstructive Disease (n = 5,043)	p Value
Age, yrs	57.4 (49.7–65.1)	56.1 (48.6–64.0)	62.1 (54.8–68.3)	<0.001
Current smoking	20.7	20.0	23.2	<0.001
Male	44.6	41.7	55.5	<0.001
Symptoms				
Typical chest pain	13	9	27	<0.001
Atypical chest pain	58	61	50	<0.001
Unspecified chest pain	22	24	15	<0.001
Dyspnea	7	6	9	<0.001
Lipid parameters, mmol/l				
Total cholesterol	5.2 (4.5–5.9)	5.2 (4.5–5.9)	5.3 (4.5–6.0)	<0.001
Low-density lipoprotein cholesterol	3.1 (2.4–3.7)	3.1 (2.4–3.7)	3.1 (2.4–3.8)	<0.001
High-density lipoprotein cholesterol	1.4 (1.2–1.8)	1.4 (1.2–1.8)	1.4 (1.1–1.7)	<0.001
Systolic blood pressure, mm Hg	132 (113–148)	131 (113–146)	137 (114–153)	<0.001
Body mass index, kg/m^2	26.2 (23.6–29.3)	26.1 (23.5–29.3)	26.4 (23.9–29.4)	<0.001
Hypertension	45.7	42.5	57.5	<0.001
Diabetes mellitus	8.5	7.4	12.2	<0.001
Comorbidity level*				<0.001
Low	69	70	65	
Moderate	18	17	19	
Severe	13	12	17	
Statin use before CTA†	27	24	37	<0.001
Aspirin use before CTA†	15	12	21	<0.001
Statin use after CTA‡	45	37	76	<0.001
Aspirin use after CTA‡	30	21	62	<0.001
Agatston calcium score	0 (0–57)	0 (0–14)	124 (21–329)	<0.001

Values are median (interquartile range) or %. *Levels of comorbidity were based on Charlson comorbidity index scores of 0 (low), 1 (moderate), and ≥ 2 (severe). †First statin or aspirin prescription occurring >90 days before computed tomography angiography (CTA). ‡Statin or aspirin prescription within 90 days after CTA.

FIGURE 1 Relationship Between Increasing Coronary Artery Calcium Burden and the Presence of Coronary Vessels With Obstructive Disease



With increasing coronary artery calcium (CAC) burden, the prevalence of obstructive coronary artery disease (CAD) increased stepwise.

METHODS

PATIENTS. The WDHR provided data for this cohort study (10,13). This data source has been audited and validated (14). In Western Denmark, CTA is the first-line diagnostic test for nonemergency patients with symptoms suggesting CAD (15). Our study included all patients >18 years of age who underwent CTA between January 1, 2008, and December 31, 2017, in Western Denmark because of symptoms suggestive of CAD. Exclusion criteria were known CAD (prior MI or coronary revascularization) or a missing CTA result. The Danish National Health Service provides universal tax-supported health care as well as partial reimbursement for costs of prescribed medications. A Civil Personal Registration (CPR) number is assigned to each Danish citizen at birth. This allowed accurate linkage of information among the medical and administrative registries used in this study (16).

The study was approved by the Danish Data Protection Agency (record numbers: 2008-58-0035 and 2012-41-0914) and the regional ethics committee.

ANGIOGRAPHY ACQUISITION AND SEVERITY OF CAD. CTA was performed with different CT scanner platforms (Siemens Healthineers [Erlangen, Germany], Toshiba [Ōtawara, Tochigi, Japan], and Philips Healthcare [Best, the Netherlands]) with ≥64-slice detector rows. CTA image acquisition was performed according to CTA best practice guidelines (7). For the present study, we categorized CAD severity based on: 1) obstructive disease; and 2) calcified atherosclerotic burden classifications. In the classification based on presence of obstructive disease, we defined the following groups: "no CAD" (0% luminal stenosis and Agatston CAC score = 0), "nonobstructive CAD" (<50% luminal stenosis), or "obstructive CAD" (>50% luminal stenosis). Patients with obstructive disease were divided further into groups according to presence of 1-, 2-, or 3-vessel obstructive CAD. In the classification based on calcified atherosclerotic burden, we defined the following groups (CAC score = 0, CAC score = 1 to 99, CAC score = 100 to 399, CAC score = 400 to 1,000, and CAC score >1,000) regardless of whether patients had nonobstructive or obstructive CAD.

TABLE 2 Relation Between Coronary Artery Calcium/Number of Vessels With Obstructive Disease With Clinical Events >90 Days After CTA

		MI, Stroke, and All-Cause Death		
Atherosclerosis Measurement	n	n (%)	Event Rate per 1,000 Person-Yrs	Hazard Ratio*
CAC burden				
CAC = 0	12,771	349 (3)	6.2 (5.6–6.9)	1 (reference)
CAC 1 to 99	6,408	302 (5)	11.2 (10.0–12.5)	1.3 (1.1–1.5)
CAC >100 to 399	3,163	228 (7)	17.5 (15.4–20.0)	1.7 (1.4–2.1)
CAC >400 to 1,000	1,053	118 (11)	29.1 (24.3–34.9)	2.6 (2.1–3.2)
CAC >1,000	364	55 (15)	42.3 (32.1–54.4)	3.4 (2.5–4.6)
Vessels with obstruction				
No CAD	11,107	304 (3)	6.1 (5.4–6.8)	1 (reference)
Nonobstructive CAD	7,604	384 (6)	12.3 (11.1–13.5)	1.3 (1.1–1.6)
1-vessel obstructive CAD	3,462	210 (6)	14.9 (13.0–17.1)	1.6 (1.3–1.9)
2-vessel obstructive CAD	1,131	93 (8)	20.0 (16.3–24.5)	1.9 (1.5–2.4)
3-vessel obstructive CAD	450	63 (14)	34.7 (27.1–44.4)	2.9 (2.2–3.9)

*Adjusted for age and sex.
CAC = coronary artery calcium; CTA = computed tomography angiography; MI = myocardial infarction.

COMORBIDITY ASSESSMENT AND MAJOR CVD ENDPOINTS. Based on diagnosis codes, a Charlson comorbidity index (CCI) score was computed for each patient (Supplemental Table 1), and comorbidity was categorized as low (CCI score = 0), moderate (CCI score = 1), or severe (CCI score ≥ 2).

The primary endpoint was MI, stroke, or all-cause death occurring >90 days after the CTA until the end of follow-up. Events occurring within 90 days was excluded. In additional analyses, only MI and stroke were included. The study outcomes were identified through linkage among national registries covering all Danish hospitals (17). Data on prescribed medications were retrieved from the Danish National Health Service Prescription Database (18), with baseline medication use defined as redeemed prescriptions during the 6 months prior to the CTA, and post-CTA medication use defined as prescriptions redeemed after the examination. Data on clinical outcomes were obtained from the Danish National Registry of Patients and the Civil Registration System, as previously described (15).

STATISTICAL ANALYSES. Analyses were performed using Stata version 15.1 SE (StataCorp LP, College Station, Texas). Baseline characteristics are presented as proportions for categorical variables and as medians (interquartile range) for continuous variables. We followed all patients from 90 days after the date of their CTA examination until occurrence of 1 of the adverse events (MI, stroke, or all-cause death) or end of follow-up on July 6, 2018. No patients were lost to follow-up.

Prevalence of no or nonobstructive disease, 1-vessel CAD, 2-vessel CAD, as well as 3-vessel CAD were calculated and stratified by the CAC burden groups (CAC = 0, CAC 1 to 99, CAC 100 to 399, CAC 400 to 1,000, and CAC >1,000).

We calculated the CVD event rates per 1,000 person-years (with 95% confidence intervals [CIs]) across the different CAD classification groups, and we stratified the analyses by the presence versus absence of obstructive stenoses. Further, Cox proportional regression modeling analyzing time to first event was used to compute multivariable-adjusted hazard ratios for increasing CAD severity (using both obstructive disease and atherosclerosis burden classifications). The proportional hazard assumption was assessed using Schoenfeld residuals and was met for all models. These analyses were adjusted for age, sex, smoking, diabetes, Charlson Comorbidity Index, low-density lipoprotein cholesterol, CAC score, post-CTA statin (defined as statin prescription within 90 days after CTA) and aspirin use (defined as aspirin prescription within 90 days after CTA).

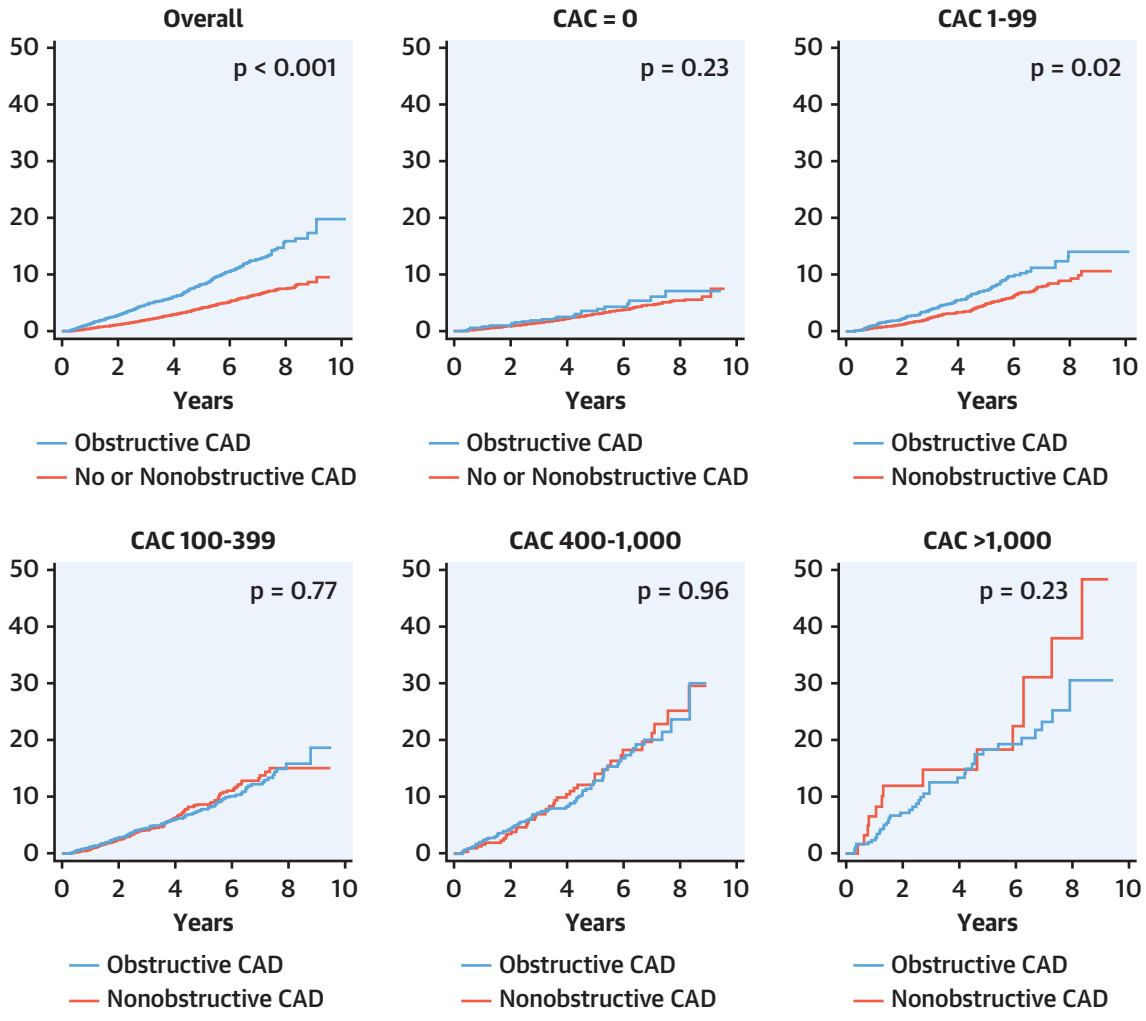
We performed additional analysis to validate our findings. First, we restricted clinical outcome to MI and stroke only. Second, to make sure that the results were not caused by differences in initial revascularization of patients with obstructive CAD, we performed analyses excluding individuals who underwent percutaneous coronary intervention and coronary artery bypass grafting within 90 days of CTA.

RESULTS

Baseline characteristics and the distribution of study patients with obstructive and nonobstructive CAD are presented in **Table 1**. Among the 23,759 symptomatic patients in the study population, 18,716 were diagnosed with no or nonobstructive disease and 5,043 with obstructive CAD. Pre-CTA statin and aspirin use was similar in patients with no or nonobstructive CAD versus obstructive CAD when stratified by calcified atherosclerotic burden as assessed by CAC scores (Supplemental Table 2). During a median of 4.3 years (interquartile range: 2.4 to 6.1 years) of follow-up, 1,054 patients experienced a first event (MI [n = 219], stroke [n = 299], or death [n = 536]).

PREVALENCE OF OBSTRUCTIVE DISEASE STRATIFIED BY CAC SCORE. The prevalence of obstructive CAD increased with increasing CAC scores (**Figure 1**). Among patients with a CAC score of 0, 87% had no CAD, 7% had nonobstructive CAD, and 6% had obstructive CAD. The corresponding proportions were 3%, 14%, and 83%, respectively, for patients with CAC

FIGURE 2 Cumulative Incidence of CVD and Death in Patients With Nonobstructive Versus Obstructive CAD Stratified by Atherosclerosis Burden



Clinical events included myocardial infarction, stroke, and all-cause death. CVD = cardiovascular disease; other abbreviations as in Figure 1.

scores >1,000. Both the prevalence of obstructive CAD and the number of vessels with obstructive disease increased with calcified atherosclerotic burden (Figure 1). Most patients with obstructive CAD, however, had CAC scores of 100 to 399 (Supplemental Figure 1).

CVD EVENT RATES ACCORDING TO CAC SCORE AND OBSTRUCTIVE VESSEL DISEASE. Overall, the risk of major CVD events increased stepwise with both atherosclerotic disease burden and number of vessels with obstructive disease (Table 2). For atherosclerotic disease burden, the event rate per 1,000 person-years ranged from 6.2 (95% CI: 5.6 to 6.9) among patients with a CAC score of 0 to 42.3 (95% CI: 32.1 to 54.4) among patients with CAC score >1,000 (Table 2). Similarly, based on the number of vessels with obstructive disease, the event rate per 1,000 person-years increased from 6.1 (95% CI: 5.4 to 6.8) in patients with no CAD to 34.7 (95% CI: 27.1 to 44.4) in patients with 3-vessel obstructive disease (Table 2).

CVD EVENT RATES STRATIFIED BY PRESENCE VERSUS ABSENCE OF OBSTRUCTIVE VESSEL DISEASE. Because we found that calcified atherosclerotic burden and prevalence of obstructive CAD were highly correlated (Figure 1), we performed additional analyses to assess the relative importance of calcified atherosclerotic burden versus obstructive stenoses. Stratification by atherosclerosis burden, as defined by the 5 CAC

TABLE 3 Association of Obstructive Stenoses With Risk of Major Cardiovascular Events and Death Occurring >90 Days After CTA

		MI, Stroke, and All-Cause Death		
Atherosclerosis Measurement	n (%)	n (%)	Event Rate Per 1,000 Person-Yrs	Hazard Ratio*
CAC = 0				
No or nonobstructive CAD	12,046	324	6.1 (5.5–6.8)	1 (reference)
Obstructive CAD	725	25	7.2 (5.2–11.3)	0.9 (0.6–1.4)
CAC 1–99				
Nonobstructive CAD	4,856	204	10.0 (8.7–11.4)	1 (reference)
Obstructive CAD	1,552	98	15.2 (12.4–18.6)	1.3 (1.0–1.6)
CAC >100–399				
Nonobstructive CAD	1,433	105	17.9 (14.8–21.7)	1 (reference)
Obstructive CAD	1,730	123	17.3 (14.5–20.6)	1.1 (0.8–1.4)
CAC >400–1,000				
Nonobstructive CAD	318	41	30.2 (22.2–41.0)	1 (reference)
Obstructive CAD	735	77	28.6 (22.9–35.7)	0.9 (0.6–1.4)
CAC >1,000				
Nonobstructive CAD	63	14	57.9 (34.3–97.8)	1 (reference)
Obstructive CAD	301	41	38.8 (28.8–52.3)	0.6 (0.3–1.1)

*Adjusted for age, sex, smoking, diabetes, level of comorbidity based on Charlson comorbidity index score (0 = low, 1= moderate, and ≥2 = severe), low-density lipoprotein cholesterol, systolic blood pressure, CAC score, post-CTA statin use, and post-CTA aspirin use.

MI = myocardial infarction; other abbreviations as in Table 1.

groups, showed that patients with nonobstructive CAD generally had a similar risk of major CVD events and death as patients with obstructive CAD (**Figure 2, Table 3**). For example, among patients with CAC scores of 100 to 399, the event rate per 1,000 person-years was 17.9 (95% CI: 14.8 to 21.7) in patients with nonobstructive CAD and 17.3 (95% CI: 14.5 to 20.6) in patients with obstructive CAD. Similar results were found for CAC scores of 0, 400 to 1,000, and >1,000. Among patients with CAC scores of 1 to 99, those with obstructive CAD had higher event rates than those with nonobstructive CAD. Cox regression modeling adjusting for baseline characteristics and CAC score showed that presence of obstructive CAD was not associated with increased risk of major CVD events in all groups defined by increasing CAC scores, except for CAC 1 to 99 where obstructive stenoses was associated with ≈30% increased risk (**Table 3, Central Illustration**). Further, dividing obstructive CAD into 1-, 2- and 3-vessel CAD did not show any significant trend toward higher risk in patients with multivessel obstructive CAD compared with nonobstructive CAD when stratified by CAC burden (Supplemental Table 3).

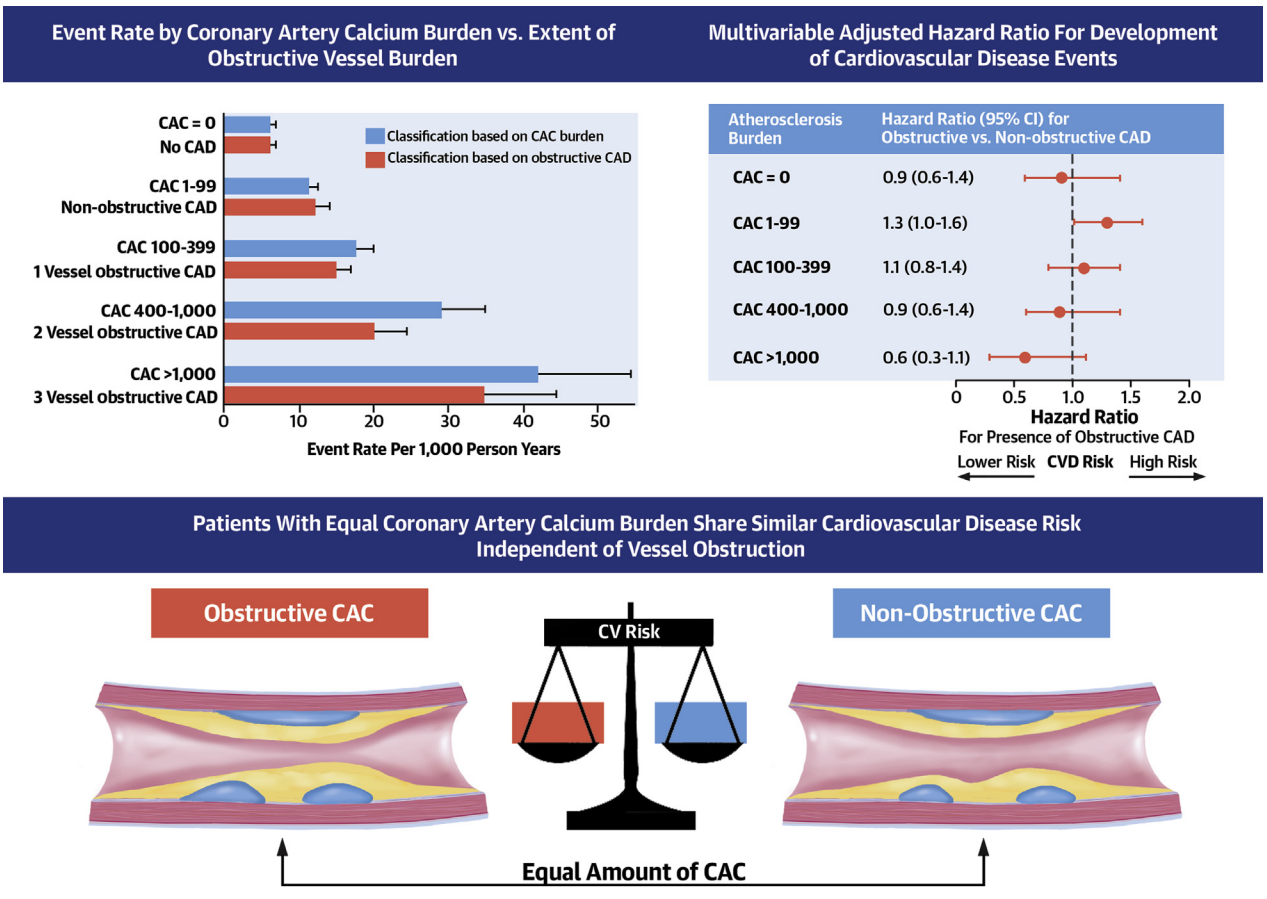
ROBUSTNESS OF RESULTS FOR OTHER ENDPOINTS AND DIFFERENT STUDY POPULATIONS. First, as calcium may represent a more stable versus aggressive phenotype in older and younger individuals, respectively, we performed analyses in patients age ≤65 and >65 years separately. As shown in Supplementary Tables 4 to 7, the results were similar to the main analyses with no substantial independent increase in risk conferred by obstructive CAD. Further, as CAC scores have shown to be associated with all-cause mortality risk, including mortality from causes other than cardiovascular causes, we reanalyzed the results using MI and stroke as endpoints (excluding all-cause death). As seen in Supplemental Figure 1 and Supplemental Tables 8 and 9, the results were similar to those for the main analyses. The risk for MI and stroke increased stepwise with both: 1) increasing calcified atherosclerotic burden; and 2) number of vessels with obstructive disease. Further, for similar degrees of calcified atherosclerotic burden, patients with nonobstructive CAD had risks comparable with those of patients with obstructive CAD.

To examine whether the similar risks in patients with obstructive and nonobstructive CAD could have been due to revascularization of those with obstructive CAD, we performed an additional analysis excluding patients who were revascularized within 90 days of CTA. As seen in Supplemental Figures 2 to 4 and Supplemental Tables 10 and 11, the results were similar to those in the main analyses. Similarly, considering revascularization at any time during follow-up as a time-varying covariate yielded comparable results (Supplemental Tables 12 and 13), demonstrating that revascularizations did not change the results. Further, we reanalyzed the results including events occurring within the first 90 days of CTA. As shown in Supplemental Tables 14 and 15, the results were similar to the main analyses. Finally, there was no clear trend in the association of post-CTA statin use and major CVD events in crude analyses (Supplemental Figure 5).

DISCUSSION

The present study, based on a large contemporary cohort of consecutive patients undergoing CTA testing according to medical society guidelines, provides important new insights into the relative contributions of atherosclerotic plaque burden and stenoses to risk of subsequent major CVD events. We observed a stepwise increase in risk with both increasing calcified atherosclerotic burden and number of vessels with obstructive CAD. However, when stratified by calcified atherosclerotic burden, the risk of major CVD events was comparable in patients with obstructive and nonobstructive CAD (**Central Illustration**). These results were consistent in analyses that: 1) excluded

CENTRAL ILLUSTRATION **Atherosclerosis Plaque Burden, Not Stenoses Per Se, Is the Main Predictor of Risk for Cardiovascular Disease Events in Patients With Stable Coronary Artery Disease**



Mortensen, M.B. et al. J Am Coll Cardiol. 2020;76(24):2803–13.

(Top left) Risk for major cardiovascular disease (CVD) events increases stepwise with both atherosclerotic plaque burden as assessed by coronary artery calcium (CAC) and with number of vessels with obstructive coronary artery disease (CAD). **(Top right)** However, when stratified by groups of CAC burden, patients with obstructive versus nonobstructive CAD had similar CVD event rates. **(Bottom)** For the same atherosclerotic plaque burden, patients with nonobstructive CAD have a similar risk for CVD as patients with obstructive CAD.

death from the endpoint; and 2) excluded patients who were revascularized within the first 90 days of their CTA scan. Taken together, this suggests that calcified atherosclerotic burden, not stenosis, is the main predictor of future CVD events and death in patients with CAD. Further, it shows that the traditional dichotomous definition of CAD as "obstructive" or "nonobstructive" is inadequate for identifying truly high-risk patients who may benefit from intensive secondary preventive therapies.

In current guidelines and clinical practice, diagnosis and management of coronary heart disease center on presence of at least 1 epicardial coronary stenosis >50% or presence of provocable ischemia with a stress test (3,19). Affected patients are known to be at high risk for subsequent major CVD events and are therefore recommended to receive intensive secondary prevention therapies and possibly revascularization (20). In contrast, patients without obstructive CAD are assumed to be at lower risk for major CVD events, with no clear recommendations for management.

With the advent of CTA, obstructive as well as nonobstructive atherosclerotic plaques now can be detected and quantified easily. However, the implications of varying degrees of nonobstructive CAD for subsequent risk, as well as any difference in risks for patients with nonobstructive versus obstructive CAD,

remain unclear. This study showed that there is a high correlation between CAC—a crude marker of overall atherosclerotic burden—and presence of obstructive stenoses, with higher plaque burden increasing the probability of multivessel obstructive CAD. Previous angiography studies have reported similar results (21). Thus, the well-known association between the number of vessels with obstructive stenoses and subsequent risk of major CVD events theoretically can be caused by either stenosis alone, total plaque burden alone (due to the high correlation), or by a combination of both (12). Until now, it has remained unclear which condition explains most of the risk. A previous report among 7,540 patients without chest pain from the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes) registry showed that CTA information on number of vessels with obstructive CAD did not improve CVD risk discrimination (c-statistics) when CAC was already included in the prediction model (22). However, due to the high correlation between CAC scores and number of stenoses, the study could not identify which of these features explained most of the risk. Other studies using both CTA and invasive angiography have shown that patients with nonobstructive CAD are at high risk for CVD—in some situations comparable to risk among patients with obstructive CAD (23–26).

Our study adds to the existing published data by demonstrating that for a given atherosclerotic burden, the risk of major CVD events and death was generally not substantially affected by presence of obstructive CAD. This was consistent across the spectrum of calcified atherosclerotic burden, ranging from absence of detectable CAC to CAC scores >1,000. Among patients with limited CAC (scores of 1 to 99), those with obstructive CAD had higher event rates than patients with nonobstructive CAD. However, in this CAC group, patients with obstructive CAD had a median CAC score that was 85% higher than the median CAC score in patients with nonobstructive CAD (data not shown). This may explain part of the increased event rate in the obstructive CAD group, but a ≈30 higher relative risk remained after adjusting for CAC and baseline characteristics indicating that obstructive CAD provides incremental value when CAC is moderate. Furthermore, and just as importantly, patients with extensive nonobstructive CAD (i.e., CAC scores of 400 to 1,000) had higher event rates than patients with obstructive CAD but less extensive calcified atherosclerotic burden (i.e., CAC scores of 100 to 399). These findings indicate that the prognostic information conferred by presence of obstructive CAD is primarily due to its correlation with atherosclerotic burden and not to the stenoses per se. This is in line with pathological and clinical studies revealing that most atherosclerotic lesions that trigger acute thrombotic events (i.e., MIs) have <50% lumen narrowing before the event. Thus, they arise from areas with nonobstructive plaques (8,27–30). Our results are generally in agreement with a prior study of 8,627 symptomatic patients from the CONFIRM showing that presence of obstructive CAD only moderately improved discrimination in those with CAC <100, but not in those with CAC >100 (i.e., indicating limited independent value of obstructive CAD when CAC is >100) (31). Despite these agreements, patients with obstructive CAD and CAC 1 to 100 in the CONFIRM study had considerably higher event rates than patients with nonobstructive CAD. The reasons for this apparent discrepancy between the 2 studies may include longer follow-up time in our analyses (52 weeks vs. 25 weeks), differences in initial management of patients with obstructive CAD (i.e., differences in revascularization procedures), and that our primary analyses included stroke in the endpoint.

Identifying high-risk patients with nonobstructive CAD is of paramount importance for overall CVD prevention. As shown in our study, the vast majority (≈65%) of events occurred among patients who did not have obstructive CAD. Analyses from the PROMISE (PROspective Multicenter Imaging Study for Evaluation of Chest Pain) study showed that >50% of adverse events occurred in patients with normal stress test findings (i.e., no provocable ischemia) (32). The apparent paradox that most events occur in patients with nonobstructive CAD than in patients with obstructive CAD is explained by the fact that many more individuals have nonobstructive than obstructive CAD. Therefore, recommendations on how physicians should allocate preventive treatment to patients with nonobstructive CAD is needed. Given the plethora of medications available for primary prevention, understanding risk and intensification of medical therapy based upon the atheroma findings is of critical importance

The usefulness of CTA in guiding appropriate preventive therapies has been investigated previously. For example, a substudy from the CONFIRM registry suggested that statin therapy was associated with lower mortality in patients with nonobstructive CAD as assessed by CTA (33). Similarly, Hulten et al. (34) found trends toward a substantial reduction in cardiovascular death or MI with statin therapy among patients with nonobstructive CAD. Further, Mitchell

et al. (35) found that severity of CAC could be used to identify patients most likely to benefit from statins. Although these were observational CTA studies with potential biases, the recent prospective randomized controlled SCOT-HEART (Scottish COmputed Tomography of the HEART) trial confirmed the ability of CTA to improve downstream use of preventive therapy that, ultimately, was associated with a roughly 45% relative risk reduction of fatal and nonfatal MI (36,37). Thus, accumulating evidence supports the use of CTA to guide individualized preventive treatment among patients with obstructive as well as nonobstructive CAD.

The results indicating that obstructive stenoses per se do not increase risk may provide some of the explanation as to why alleviating stenoses in RCTs such as COURAGE (Optimal Medical Therapy with or without PCI for Stable Coronary Disease), FAME-II (Fractional Flow Reserve-Guided PCI versus Medical Therapy in Stable Coronary Disease), and ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) did not provide significant reduction of major CVD events in stable patients (38–40). Although these trials documented that initial revascularization reduced the number of subsequent revascularization procedures as well as reduced overall angina symptoms, it had no or minimal effect on major CVD endpoints including MI and death beyond what was achieved by optimal medical therapy alone. Viewed in this context, first-line use of CTA with possibly selective CTA derived physiological adjudication (10) in symptomatic patients provide key opportunities for both selecting the most optimal patients with obstructive CAD for the catheterization laboratory, but also for tailoring pharmacological treatment among patients with obstructive and nonobstructive CAD aimed at preventing future hard CVD events in individuals at truly high risk.

STUDY LIMITATIONS. First, our study was observational. Although we adjusted our Cox analyses for baseline characteristics (including the Charlson comorbidity index) and post-CTA use of statins and aspirin in Cox analyses, potential uncontrolled confounders could still be present. Second, we did not have access to other markers of atherosclerotic phenotype, such as adverse plaque characteristics, the segment involvement score, volume scores, or Hounsfield unit density. Such additional measures, used in conjunction with CAC scores, may further improve risk stratification among patients with CAD. Third, the analysis was performed on a per-patient basis, rather than a per-vessel or -lesion basis, thus precluding whether the obstructive CAD is, in fact, the dangerous lesion. Fourth, the diagnostic accuracy of CTA may decline with increasing CAC score levels. However, centers reporting to the WDHR follow societal guidelines on best CT acquisition, and CTA is performed on high-end scanners with high temporal and spatial resolution and new CT applications, such as advanced iterative reconstructions. Moreover, CTA is performed only in patients with a high probability of a diagnostic result (considering calcification, patient corporation and arrhythmia, and so on). Thus, impaired diagnostic accuracy of stenosis severity in patients with severe calcification most likely had limited influence on the results. This is supported by the fact that findings were consistent across all CAC score groups. Fifth, some referral bias may exist as those with reasons to not undergo CTA would not be included (i.e., known CVD, severe kidney disease) Finally, we defined obstructive CAD as luminal stenoses >50% and other definitions may have yielded different results. However, the number of vessels with luminal stenoses >50% was strongly associated with stepwise increase in CVD risk in our analyses.

A major strength of this study is that the data stemmed from a large all-comer real-world practice cohort. We were able to adjust our Cox models for major risk factors and differences in post-CTA statin and aspirin use between patients with obstructive and nonobstructive CAD to assess the independent impact of obstructive CAD on subsequent risk. Further, no patients were lost to follow-up. Finally, the results were robust in analyses using other endpoint or patient selection.

CONCLUSIONS

Total coronary atherosclerotic plaque burden, not presence of stenoses per se, is the main predictor of risk for future CVD events and death in patients with CAD. Thus, when overall calcified plaque burden is similar, patients with nonobstructive and obstructive CAD are generally at similar risk. These results challenge the current paradigm of secondary prevention, in which patients are selected for intensive pharmacological prevention and subsequent revascularization procedures based mainly on presence of obstructive CAD. Further, our findings support first-line use of CTA in the diagnostic work-up of patients with symptoms suggestive of CAD, as it provides key opportunities for individualizing preventive interventions to patients at high risk of major CVD events.

AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The burden of coronary atherosclerosis is a more important predictor of major adverse cardiovascular events than the severity of arterial stenosis as assessed by CTA.

TRANSLATIONAL OUTLOOK: An assessment of coronary plaque burden should be included in studies of clinical management strategies for high-risk patients identified by CTA.

REFERENCES

1. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368:2004–13.

2. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res 2014;114:1852–66.

3. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019;100:106.

4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:e285–350.

5. National Institute for Health and Care Excellence (NICE). Clinical Guideline CG181: Lipid modification - Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. National Clinical Guideline Centre, July 2014. Available at: https://www.nice.org.uk/guidance/cg181. Accessed November 16, 2020.

6. Kelion AD, Nicol ED. The rationale for the primacy of coronary CT angiography in the National Institute for Health and Care Excellence (NICE) guideline (CG95) for the investigation of chest pain of recent onset. J Cardiovasc Comput Tomogr 2018;12:516–22.

7. Abbara S, Blanke P, Maroules CD, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr 2016;10:435–49.

8. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009;54:49–57.

9. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–81.

10. Nielsen LH, Bøtker HE, Sørensen HT, et al. Prognostic assessment of stable coronary artery disease as determined by coronary computed tomography angiography: a Danish multicentre cohort study. Eur Heart J 2017;38:413–21.

11. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of estimated 10-year risk of recurrent vascular events and residual risk in a secondary prevention population. Circulation 2016;134:1419–29.

12. Arbab-Zadeh A, Fuster V. The risk continuum of atherosclerosis and its implications for defining CHD by coronary angiography. J Am Coll Cardiol 2016;68:2467–78.

13. Schmidt M, Mæng M, Madsen M, Sørensen HT, Jensen LO, Jakobsen C-J. The Western Denmark Heart Registry: its influence on cardiovascular patient care. J Am Coll Cardiol 2018;71:1259–72.

14. Nielsen LH, Nørgaard BL, Tilsted HH, et al. The Western Denmark Cardiac Computed Tomography Registry: a review and validation study. Clin Epidemiol 2015;7:53–64.

15. Nørgaard BL, Terkelsen CJ, Mathiassen ON, et al. Coronary CT angiographic and flow reserve-guided management of patients with stable ischemic heart disease. J Am Coll Cardiol 2018;72:2123–34.

16. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541–9.

17. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol 2019;11:563–91.

18. Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, Schmidt M, Pedersen L, Sørensen HT. Existing data sources for clinical epidemiology: the Danish National Database of Reimbursed Prescriptions. Clin Epidemiol 2012;4:303–13.

19. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2014;64:1929–49.

20. Mortensen MB, Blaha MJ, Nordestgaard BG. Eligibility and preventive potential for new evidence-based cardiovascular drugs in secondary prevention. JAMA Cardiol 2020;5:209.

21. Nakagomi A, Celermajer DS, Lumley T, Freedman SB. Angiographic severity of coronary narrowing is a surrogate marker for the extent of coronary atherosclerosis. Am J Cardiol 1996;78:516–9.

22. Cho I, Chang H-J, Sung JM, et al. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry). Circulation 2012;126:304–13.

23. Mushtaq S, De Araujo Gonçalves P, Garcia-Garcia HM, et al. Long-term prognostic effect of coronary atherosclerotic burden: validation of the computed tomography-Leaman score. Circ Cardiovasc Imaging 2015;8:e002332.

24. Bittencourt MS, Hulten E, Ghoshhajra B, et al. Prognostic value of nonobstructive and obstructive coronary artery disease detected by coronary computed tomography angiography to identify cardiovascular events. Circ Cardiovasc Imaging 2014;7:282–91.

25. Maddox TM, Stanislawski MA, Grunwald GK, et al. Nonobstructive coronary artery disease and

risk of myocardial infarction. JAMA 2014;312:1754–63.

26. Jespersen L, Hvelplund A, Abildstrom SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J 2012;33:734–44.

27. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988;12:56–62.

28. Falk E, Fuster V. Angina pectoris and disease progression. Circulation 1995;92:2033–5.

29. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

30. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015;66:337–46.

31. Al-Mallah MH, Qureshi W, Lin FY, et al. Does coronary CT angiography improve risk stratification over coronary calcium scoring in symptomatic patients with suspected coronary artery disease? Results from the prospective multicenter international CONFIRM registry. Eur Heart J Cardiovasc Imaging 2014;15:267–74.

32. Budoff MJ, Mayrhofer T, Ferencik M, et al. Prognostic value of coronary artery calcium in the PROMISE study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation 2017;136:1993–2005.

33. Chow BJW, Small G, Yam Y, et al. Prognostic and therapeutic implications of statin and aspirin therapy in individuals with nonobstructive coronary artery disease: results from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry) registry. Arterioscler Thromb Vasc Biol 2015;35:981–9.

34. Hulten E, Bittencourt MS, Singh A, et al. Coronary artery disease detected by coronary computed tomographic angiography is associated with intensification of preventive medical therapy and lower low-density lipoprotein cholesterol. Circ Cardiovasc Imaging 2014;7:629–38.

35. Mitchell JD, Fergestrom N, Gage BF, et al. Impact of statins on cardiovascular outcomes following coronary artery calcium scoring. J Am Coll Cardiol 2018;72:3233–42.

36. Newby DE, Adamson PD, et al., SCOT-HEART Investigators. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med 2018;379:924–33.

37. Adamson PD, Williams MC, Dweck MR, et al. Guiding therapy by coronary CT angiography improves outcomes in patients with stable chest pain. J Am Coll Cardiol 2019;74:2058–70.

38. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.

39. de Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.

40. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020;382:1395–407.

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