ORIGINAL RESEARCH

Practice Pattern, Diagnostic Yield, and Long-Term Prognostic Impact of Coronary Computed Tomographic Angiography

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BACKGROUND: Although guidelines recommend the use of coronary computed tomographic angiography (CTA) in patients with stable pain syndromes, the clinical benefits of the use of coronary CTA in a broad spectrum of patients is unknown. We evaluated the contemporary practice pattern and diagnostic yield of coronary CTA and their impact on the subsequent diagnostic-therapeutic cascade and clinical outcomes.

METHODS AND RESULTS: We identified 39 906 patients without known coronary artery disease (CAD) who underwent coronary CTA between January 2007 and December 2013. The patients' demographic characteristics, risk factors, symptoms, results of coronary CTA, the appropriateness of downstream diagnostic and therapeutic interventions, and long-term outcomes (death or myocardial infarction) were evaluated. The number of coronary CTAs had increased over time, especially in asymptomatic patients. Coronary CTA revealed that 6108 patients (15.3%) had obstructive CAD (23.7% of symptomatic and 9.3% of asymptomatic patients). Subsequent cardiac catheterization was performed in 19.2% of symptomatic patients (appropriate, 80.6%) and in 3.9% of asymptomatic patients (appropriate, 7.9%). The 5-year rate of death or myocardial infarction was significantly higher in patients with obstructive CAD on CTA than those without (7.2% versus 3.0%; $P<0.001$; adjusted hazard ratio [95% CI], 1.34 [1.17–1.54]). However, obstructive CAD on CTA had limited added value over conventional risk factors for predicting death or myocardial infarction.

CONCLUSIONS: Although the use of coronary CTA had substantially increased, CTA had a low diagnostic yield for obstructive CAD, especially in asymptomatic patients. The use of CTA in asymptomatic patients seemed to have led to inappropriate subsequent diagnostic or therapeutic interventions without clinical benefit.

Key Words: cardiovascular outcomes ■ coronary artery bypass grafting ■ coronary computed tomographic angiography ■ percutaneous coronary intervention

Because coronary artery disease (CAD) has a high prevalence and lacks specific diagnostic clinical signs and symptoms, guidelines recommend coronary computed tomographic angiography (CTA) in patients with stable pain syndromes who show moderate pretest risks of obstructive CAD.[1,2] The goal of these recommendations is to prevent patients with low risks of obstructive CAD from undergoing unnecessary coronary CTA, thereby enhancing the diagnostic yield and clinical usefulness of coronary CTA as well as reducing test-related costs and risks. Because CTA provides a direct anatomic assessment of CAD with substantially higher accuracy compared with functional testing,[3,4] the use of coronary CTA has substantially increased and is widely used as a frontline noninvasive diagnostic tool for the detection of obstructive CAD.

CLINICAL PERSPECTIVE

What Is New?

- The contemporary practice patterns and diagnostic yield of coronary computed tomographic angiography and its impact on the subsequent diagnostic-therapeutic cascade and long-term clinical outcomes are yet to be clarified.
- In this large-sized observational cohort, coronary computed tomographic angiography had increased in its use but showed limited clinical benefits, such as low diagnostic yield for obstructive coronary artery disease, low proportion of appropriate subsequent invasive procedures, and small additive effect on the prognosis for death or myocardial infarction.

What Are the Clinical Implications?

- Given that coronary computed tomographic angiography showed a limited role as a screening test in contemporary practice, a more adequate pretest clinical assessment is essential to discriminate the minimal-risk patients for whom deferred testing may be considered, and to reduce the potential risks stemming from radiation exposure and subsequent invasive procedures.

Nonstandard Abbreviations and Acronyms

CAG	coronary angiography
CTA	computed tomographic angiography
PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
SCOT-HEART	Scottish Computed Tomography of the Heart

Another potential benefit of CTA is the reduction in the need for invasive cardiac catheterization, which has a low diagnostic yield in routine clinical practice.[5] On the basis of such usefulness and reliability of CTA, the recently updated guidelines recommend coronary CTA as the first-line test or class 1 recommendation for the evaluation of patients with suspected stable CAD or atypical symptoms.[6,7]

Nevertheless, the overuse of coronary CTA may be a potentially significant health problem, considering the possibility of radiation hazard as well as increases in the number of downstream invasive cardiac procedures and CAD-related costs.[8,9] Particularly, in asymptomatic patients, unnecessary use of coronary CTA could have a negative net effect if the overall

benefits by the coronary CTA are not readily apparent. The contemporary patterns of coronary CTA use and their impact on subsequent diagnostic or therapeutic management and clinical outcomes are yet to be clarified. We therefore evaluated the current practices and diagnostic yield of coronary CTA as measured by the prevalence of obstructive CAD, and examined the associations among clinical risk factors, presenting symptoms, results of subsequent catheterization, and the long-term prognostic impact of coronary CTA.

METHODS

The data related to the findings of this study are available from the corresponding author on reasonable request.

Study Population

This study was conducted in the context of a prospective observational registry. We evaluated consecutive patients who underwent coronary CTA between March 1, 2007, and December 31, 2013, at Asan Medical Center, which is a large-sized tertiary referral hospital in Seoul, South Korea. To selectively analyze patients without known or documented heart diseases, we excluded those with a history of myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), cardiac transplantation, or valvular surgery.

We collected information on the patients' demographic characteristics, clinical risk factors, comorbid conditions, laboratory findings, and concomitant cardiovascular medications. Cardiac symptoms at the time of coronary CTA were categorized as symptomatic or asymptomatic (including no angina). The patients were considered symptomatic if they had symptoms related to CAD (eg, chest pain, chest tightness, chest discomfort, dyspnea, exertional dyspnea, and shortness of breath). To estimate the baseline cardiovascular risks of each individual, the Framingham risk score for hard coronary heart disease (https://www.framinghamheartstudy.org/fhs-risk-functions/hard-coronary-heart-disease-10-year-risk/) was calculated. In the subset of patients with missing values (n=4491; 11.2%), a modified Framingham risk score was calculated on the basis of available clinical data, with a moderate score (ie, 1 point) imputed for either a history of dyslipidemia or the use of statins, and for the presence of hypertension or a history of medication use for blood pressure control.[5] The risk scores were categorized as low (<10%), intermediate (10%–20%), or high (>20%) according to the predicted risk of hard coronary heart disease. The institutional review board at Asan Medical Center approved the use of clinical data for

this study, and all patients provided written informed consent.

Coronary CTA and Obstructive CAD

Coronary CTA was conducted by using either a single-source 64-section computed tomography (CT) instrument (LightSpeed VCT; GE, Milwaukee, WI) or a dual-source CT instrument (Somatom Definition; Siemens, Erlangen, Germany).[10,11] All coronary CTA scans were analyzed using a dedicated workstation (Volume Wizard; Siemens) by experienced cardiovascular radiologists. According to the guidelines of the Society of Cardiovascular Computed Tomography, a 16-segment coronary artery tree model was used. Obstructive CAD was defined as stenosis of ≥50% of the diameter of a major epicardial vessel. The contrast-enhanced portion of the coronary lumen was semiautomatically traced at the site of maximal stenosis. The diameter stenosis was then calculated by comparing with the mean value of the proximal and distal reference sites.[12] The extent of the CAD (1-, 2-, or 3-vessel disease) and high-risk CAD (ie, left main disease or proximal left anterior descending artery disease) were also evaluated.

Appropriateness of Subsequent Procedures and Long-Term Clinical Outcomes

The rates of subsequent diagnostic coronary angiography (CAG) and coronary revascularization (PCI or CABG) were calculated, and their diagnostic and therapeutic appropriateness was determined using the recommendations from major cardiovascular societies.[13,14] The information required for the assessment of the appropriateness of procedures, such as symptom status, disease extent, noninvasive test results, and medication status, was thoroughly reviewed. The appropriateness was independently judged by 2 cardiologists, and discordant cases were resolved by consensus with a third cardiologist. Patients were rated by the appropriate use criteria as appropriate, uncertain, and inappropriate for diagnostic or therapeutic procedures. Follow-up data were collected by a detailed review of all medical records. The cause and date of all deaths were confirmed by information gathered from the review of all available clinical records, together with the data from the national health insurance service.

The primary long-term clinical outcome was the composite of death from any cause or MI at 5 years after coronary CTA. All deaths were considered to be from cardiovascular causes, unless an unequivocal noncardiovascular cause could be established. MI was defined as either (1) an abnormal level of a cardiac biomarker (troponin or creatine kinase-MB) above the upper limit of the normal range and either ischemic discomfort lasting >10 minutes or ECG changes indicative of ischemia or infarction; or (2) new abnormal Q waves consistent with infarction.[15] Procedure-related MI after PCI or CABG was disregarded in this study. All clinical outcomes of interest were confirmed by source documentation and were adjudicated by an independent group of clinicians.

Statistical Analysis

The baseline demographic characteristics, risk factors, results of coronary CTA findings, and subsequent diagnostic or therapeutic procedures and their appropriateness were compared between patients with clinical symptoms suggestive of CAD at the time of coronary CTA and those without. Continuous variables are presented as medians and interquartile ranges, and categorical variables are presented as percentages. Continuous variables were compared with the Wilcoxon-Mann-Whitney nonparametric test, and categorical variables were compared with the χ^2 test. We assessed the temporal trends in the relative proportion of symptomatic or asymptomatic patients at the time of coronary CTA. For the comparison of temporal trends between symptomatic and asymptomatic patients, χ^2 test for linear by linear association was used. We also examined the diagnostic yield of coronary CTA showing obstructive CAD, according to symptom characteristic and cardiovascular risk category.

We compared the cumulative 5-year incidence of death or MI according to the presence of obstructive CAD on CTA. Cumulative event curves were generated by the Kaplan-Meier method and compared using the log-rank test. Multivariable Cox proportional hazard analyses were used to determine whether the presence of obstructive CAD on CTA was a statistically significant predictor of the primary composite of death or MI at 5 years after adjustment of clinically relevant risk factors. The following covariates were included in the model: Framingham risk score, body mass index, diabetes mellitus, history of cerebrovascular disease, baseline renal insufficiency, and symptoms at CTA.

To estimate the relative prognostic value of obstructive CAD on CTA in predicting the primary composite outcome of death or MI at 5 years, we constructed 4 separate models: model 1 only included the Framingham risk score, and model 2 added other clinical risk factors (ie, diabetes mellitus, body mass index, baseline renal insufficiency [creatinine clearance <60 mL/min], and history of cerebrovascular disease) to model 1. Model 3 further added the presence of documented symptoms, and model 4 added the presence of obstructive CAD on CTA. The predictive value of each model was

represented by the C-statistic. A nonparametric approach for comparing each C-statistic was used.[16]

All reported *P* values are 2 sided, and those <0.05 were considered to indicate statistical significance in all tests. All statistical analyses were performed using R software version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population and Baseline Characteristics

During the study period, 42 123 consecutive patients had undergone coronary CTA (Figure 1). Among them, 39 906 patients without known CAD who underwent coronary CTA and met inclusion/exclusion criteria were finally analyzed. The baseline characteristics of the overall population and according to the presence of clinical symptoms are shown in Table 1. Compared with patients who were asymptomatic at the time of CTA, symptomatic patients were older, had a lower proportion of men, and had a higher prevalence of

hypertension, diabetes mellitus, current smoking, dyslipidemia, renal insufficiency, or history of cerebrovascular disease (*P*<0.001 for all comparisons). Accordingly, symptomatic patients had a higher prevalence of those in the high-risk category in the Framingham risk score and those who received concomitant cardiovascular medications.

Practice Pattern and Findings of Coronary CTA

Among the patients who were evaluated for suspicious CAD by coronary CTA, the proportion of asymptomatic patients had substantially increased over the study enrollment period (*P* for trend <0.001; Figure 2). The practice pattern and the coronary CTA findings are shown in Table 2. In patients with clinical symptoms, coronary CTA was most frequently performed in the outpatient clinics. A large proportion of asymptomatic patients (63.9%) underwent coronary CTA in health screenings at the patients' own discretion, which was significantly less common in symptomatic patients (12.4%; *P*<0.001). Overall, obstructive CAD on CTA was identified in 15.3% of the patients,
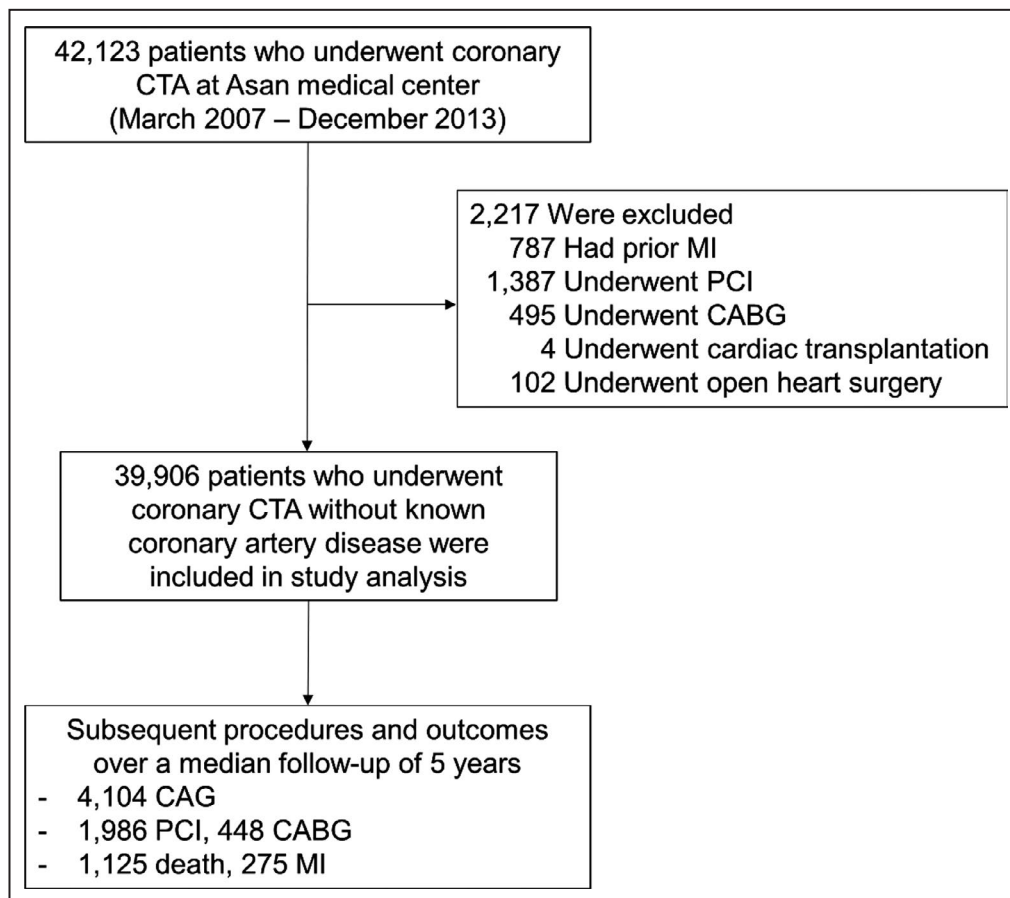

Figure 1. Study flow diagram.
CABG indicates coronary artery bypass grafting; CAG, coronary angiography; CTA, computed tomographic angiography; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

Table 1. Baseline Characteristics of the Patients

Characteristic	Total (n=39 906)	Symptomatic (n=16 571)	Asymptomatic (n=23 335)	P Value
Age, y	56.0 (50–64)	59.0 (51.0–67.0)	55.0 (50.0–61.0)	<0.001
Male sex	23 748 (59.5)	8968 (54.1)	14 780 (63.3)	<0.001
Body mass index, kg/m^2	24.5 (23.0–26.1)	24.5 (22.6–26.4)	24.5 (22.6–26.6)	0.01
Hypertension	16 844 (42.2)	8891 (53.7)	7953 (34.1)	<0.001
Systolic blood pressure, mm Hg	123.0 (111.0–134.0)	123.0 (111.0–136.0)	122.0 (112.0–133.0)	0.002
Diastolic blood pressure, mm Hg	75.0 (68.0–83.0)	74.0 (66.0–83.0)	76.0 (69.0–84.0)	<0.001
Diabetes mellitus				
Any	7247 (18.2)	3435 (20.7)	3812 (16.3)	<0.001
Insulin dependent	587 (1.5)	316 (1.9)	271 (1.2)	<0.001
Current smoker	7966 (20.0)	3627 (21.9)	4339 (18.6)	<0.001
Dyslipidemia	17 260 (43.3)	8212 (49.6)	9048 (38.8)	<0.001
Total cholesterol, mg/dL	184.0 (159.0–210.0)	179.0 (153.0–205.0)	187.0 (162.0–212.0)	<0.001
LDL cholesterol, mg/dL	115.0 (92.4–137.4)	112.2 (88.8–135.4)	116.7 (95.1–138.5)	<0.001
HDL cholesterol, mg/dL	50.0 (42.0–60.0)	48.0 (40.0–58.0)	51.0 (43.0–61.0)	<0.001
Creatinine clearance, mL/min				
Mean	85.0 (71.3–100.3)	81.7 (66.7–98.5)	86.8 (74.4–101.3)	<0.001
Creatine clearance <60 mL/min	4023 (10.1)	2487 (15.0)	1536 (6.6)	<0.001
Cerebrovascular disease	1597 (4.0)	895 (5.4)	702 (3.0)	<0.001
Framingham risk score	12 (9–14)	12 (10–15)	11 (9–13)	<0.001
Low	22 464 (56.3)	9359 (56.5)	13 105 (56.2)	
Intermediate	14 920 (37.4)	5800 (35.0)	9120 (39.1)	
High	2522 (6.3)	1412 (8.5)	1110 (4.8)	
Concurrent medications				
Aspirin	10 509 (26.3)	6182 (37.3)	4327 (18.5)	<0.001
β-Blocker	6136 (15.4)	3961 (23.9)	2175 (9.3)	<0.001
Calcium channel blocker	10 151 (25.4)	6019 (36.3)	4132 (17.7)	<0.001
ACE inhibitor or ARB	7634 (19.1)	4297 (25.9)	3337 (14.3)	<0.001
Statin	14 140 (35.4)	7332 (44.2)	6808 (29.2)	<0.001

Values are median (interquartile range) or number (percentage). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

of whom 45.3% had multivessel disease, 43.9% had proximal left anterior descending artery disease, and 8.5% had left main disease. The diagnostic yield for obstructive CAD on CTA increased with the presence of angina (23.7% of symptomatic patients and 9.3% of asymptomatic patients) and with a higher Framingham risk score (*P*<0.001 for both analyses) (Figure 3). As expected, the prevalence of multivessel, proximal left anterior descending artery and left main disease was significantly higher in symptomatic patients than in asymptomatic patients (*P*<0.001 for all comparisons).

Subsequent Procedures and Appropriateness

The rate of subsequent diagnostic or therapeutic procedures and their appropriateness are summarized in Table 3. Invasive CAG was more frequently

performed in symptomatic patients than in asymptomatic patients (19.2% versus 3.9%), and the rates of subsequent PCI (9.9% versus 1.5%) and CABG (2.4% versus 0.2%) were also significantly higher in symptomatic patients (*P*<0.001 for all comparisons). There was a substantial difference in the appropriateness of each diagnostic and therapeutic procedure according to the presence of clinical symptoms, as CAG was appropriate in most (80.6%) of patients with symptoms, but only in 7.9% of asymptomatic patients. This pattern was similar for subsequent therapeutic procedures of PCI and CABG.

Long-Term Clinical Outcomes

During a median follow-up period of 5.4 years (interquartile range, 1.3–7.4 years), the primary composite outcome of death or MI occurred in 3.4% of patients (5.2% of symptomatic patients versus 2.1% of
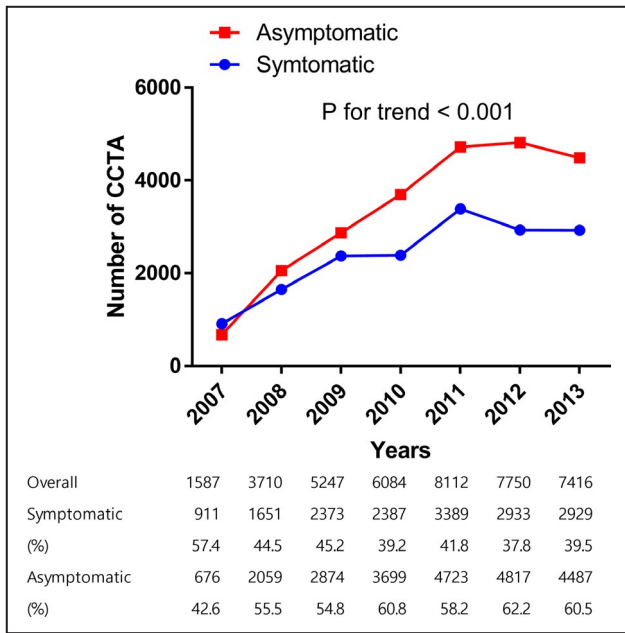
Figure 2. Temporal trends in the use of coronary computed tomographic angiography (CCTA).
Patients were considered symptomatic if they had chest pain, chest discomfort, dyspnea, or shortness of breath at performing CCTA (suspected coronary artery disease). Asymptomatic patients were defined as those without any of the above symptoms. P for trend was analyzed using χ^2 test for linear by linear association.

asymptomatic patients; P<0.001) (Table 3). The 5-year rate of primary composite outcome was significantly higher in patients with obstructive CAD on CTA than in those without, regardless of clinical symptoms

(Figure 4). Multivariable Cox regression analysis showed that the presence of obstructive CAD on CTA was independently associated with a higher risk of the primary composite of death or MI (adjusted hazard ratio, 1.34; 95% CI, 1.17–1.54), but to a lesser degree than the major clinical risk factors (Table 4).

Incremental Value of Information Obtained at Clinical Risk Assessment and CTA Findings

The results of 4 separate models for predicting the primary composite of death or MI with the information obtained from clinical assessment and CTA findings are presented in Figure 5. Model 1, which only included the Framingham risk score, had a C-statistic value of 0.595 (95% CI, 0.579–0.610). By adding clinical factors that are not included in the Framingham risk score (model 2), we obtained a C-statistic value of 0.683 (95% CI, 0.667–0.700). Model 3, which further added the presence of clinical symptoms, had a slightly higher predictive ability (C-statistic, 0.711; 95% CI, 0.695–0.726). Finally, although the presence of obstructive CAD on CTA was associated with a higher risk of the primary composite outcome, the addition of information obtained from coronary CTA (model 4) had a limited effect on the model's predictive ability over the effect achieved from the addition of clinical risk assessment (C-statistic, 0.716; 95% CI, 0.701–0.732), with a similar effect on patients with or without clinical symptoms. The calibration plot for the final model was depicted in Figure 6, which showed the agreement between predicted and observed

Table 2. Performing Site and Findings of Coronary CTA

Variables	Total (n=39 906)	Symptomatic (n=16 571)	Asymptomatic (n=23 335)	P Value
Performing site of CTA				<0.001
Outpatient clinic	17 212 (43.1)	10 345 (62.4)	6867 (29.4)	
In hospital	4002 (10.0)	2471 (14.9)	1531 (6.6)	
Emergency department	1734 (4.3)	1700 (10.3)	34 (0.1)	
Health screening	16 958 (42.5)	2055 (12.4)	14 903 (63.9)	
Coronary CTA findings				
Obstructive CAD (>50%)				<0.001
Absence	33 798 (84.7)	12 638 (76.3)	21 160 (90.7)	
Presence	6108 (15.3)	3933 (23.7)	2175 (9.3)	
Extent of obstructive CAD*				<0.001
1 Vessel	3343 (54.7)	1954 (49.7)	1389 (63.9)	
2 Vessels	1661 (27.2)	1121 (28.5)	540 (24.8)	
3 Vessels	1104 (18.1)	858 (21.8)	246 (11.3)	
Proximal LAD disease	2680 (43.9)	1882 (47.9)	798 (36.7)	<0.001
Left main disease	521 (8.5)	377 (9.6)	144 (6.6)	<0.001

Values are number (percentage). CAD indicates coronary artery disease; CTA, computed tomographic angiography; and LAD, left anterior descending artery.
*Percentages denote the proportion of subjects among patients with obstructive CAD.
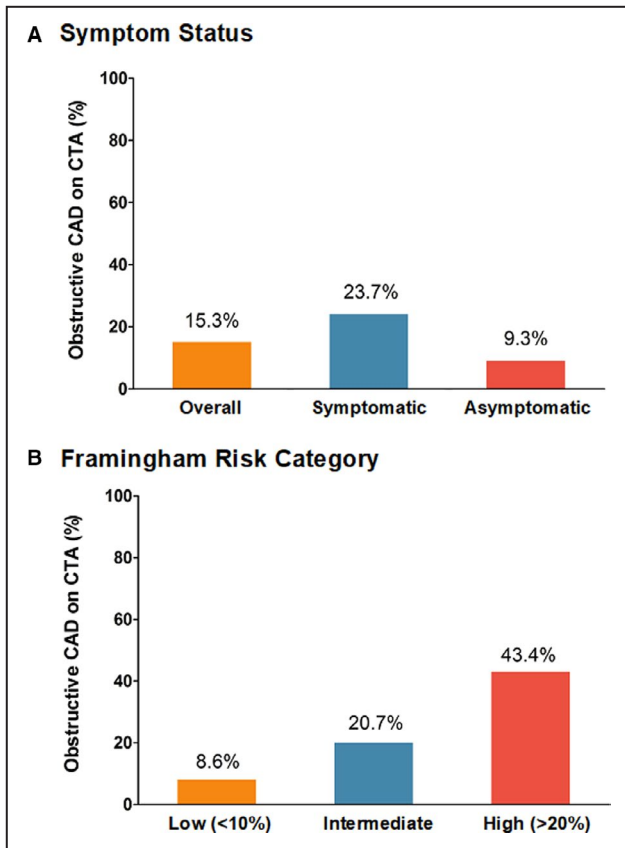
Figure 3. Patients with obstructive coronary artery disease (CAD) on coronary computed tomographic angiography (CTA) according to symptom characteristic or Framingham risk category.
Obstructive CAD was defined as >50% stenosis in a major epicardial coronary artery on coronary CTA. Results are presented according to the symptom category (overall, symptomatic, or asymptomatic) (**A**) and the level of the Framingham risk category (low, intermediate, or high) (**B**).

survival rate (calibration slope, 0.99; Brier score, 0.028). Goodness-of-fit test of prediction model was also acceptable.

DISCUSSION

In this large-sized, contemporary observational cohort of patients without known CAD who underwent coronary CTA, we found that (1) the number of patients who were evaluated with coronary CTA for detecting obstructive CAD had substantially increased over time, a trend that was more evident in asymptomatic patients; (2) CTA had a low diagnostic yield (15.3%) for obstructive CAD, and the yield was much lower in asymptomatic patients (9.3%) than in symptomatic patients (23.7%); (3) downstream invasive angiography was performed in 10.3% of the patients, which was classified as appropriate in 80.6% of symptomatic patients and only in 7.9% of asymptomatic patients; and (4)

although the presence of obstructive CAD on CTA was significantly associated with a higher risk of the primary composite of death or MI at 5 years, the incremental predictive value of obstructive CAD on CTA beyond the conventional risk score and clinical assessments was limited.

Recent advances in CT technology have significantly improved the diagnostic accuracy of coronary CTA, which led to substantial increases in its use for patients with suspected CAD.[17] During the cohort period, a single-source 64-section CT or a dual-source CT instrument was used with a mean radiation dose of ≈7.58 mSv.[11] Recently, second- or third-generation dual-source CT scanners with iterative reconstruction and high-pitch scans have been used, and technical improvements of CT (eg, prospective ECG gating, high-pitch helical acquisition, 256 or wider detector, and tube voltage reduction) have led to marked decreases in radiation exposure. With these technical advancements, several studies have reported substantial reductions in radiation dose without increases in nondiagnostic coronary CTAs.[18,19] In addition, the newer generations of iterative reconstruction algorithms improve not only the image quality but also the diagnostic accuracy in heavily calcified coronary arteries, which have acted as a major obstacle in coronary CTA.[20] Such advances of coronary CTA justify the widespread use of coronary CTA as a noninvasive alternative to CAG for the diagnosis of obstructive CAD.

Considering its high negative predictive value, CTA is commonly used to confidently rule out significant CAD in symptomatic patients with low-to-intermediate risks of CAD.[21,22] Recently, with the widespread availability of coronary CTA and its high accuracy, the scope of coronary CTA has been expanded to low-risk populations. Our study showed that CTA was widely performed in a diverse spectrum of patients, including symptomatic patients with suspicious CAD, asymptomatic high-risk patients with type 2 diabetes mellitus,[10] patients requiring preoperative cardiac evaluation for major high-risk surgery,[23] and even asymptomatic patients for self-referral health screening.[24]

The central theme of our study includes the inappropriate use of coronary CTA among asymptomatic patients. This increasing trend in the use of coronary CTA in asymptomatic patients might be an international phenomenon.[25–27] This is not in agreement with current guidelines[1,2] and is a much larger proportion than those included in other registries or trials of coronary CTA.[28–30] South Korea has a well-developed national health insurance and reimbursement system, and many hospitals therefore market health checkup programs that include CAD screening with technologically intensive cardiac CT.[31] As a result,

Table 3. Rate of Subsequent Diagnostic and Therapeutic Procedures and Clinical Outcomes After Coronary CTA

Variables	Total (n=39 906)	Symptomatic (n=16 571)	Asymptomatic (n=23 335)	P Value
CAG	4103 (10.3)	3183 (19.2)	920 (3.9)	<0.001
Appropriate		2565 (80.6)	73 (7.9)	<0.001
Uncertain		558 (17.5)	457 (49.7)	
Inappropriate		60 (1.9)	390 (42.4)	
PCI	1986 (5.0)	1636 (9.9)	350 (1.5)	<0.001
Appropriate		1006 (61.5)	133 (38.0)	<0.001
Uncertain		272 (16.6)	130 (37.1)	
Inappropriate		272 (17.4)	70 (26.1)	
CABG	448 (1.1)	403 (2.4)	45 (0.2)	<0.001
Appropriate		346 (85.9)	32 (71.1)	0.02
Uncertain		43 (10.7)	8 (17.8)	
Inappropriate		14 (3.5)	5 (11.1)	
Long-term clinical outcomes (over a median follow-up of 5 y)				
Primary composite outcome of death from any cause or MI	1370 (3.4)	869 (5.2)	501 (2.1)	<0.001
Death from any cause	1125 (2.8)	688 (4.2)	437 (1.9)	<0.001
MI	275 (0.7)	205 (1.2)	70 (0.3)	<0.001

Values are number (percentage). CABG indicates coronary artery bypass grafting; CAG, coronary angiography; CTA, computed tomographic angiography; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

CAD screening using cardiac CT or coronary CTA continues to grow in popularity. However, our study demonstrated that the benefit of routine CTA screening was poor ("pathognomonic for overdiagnosis and overtreatment") and we did not find sufficient evidence that early detection of CAD led to improved outcomes. Specifically, coronary CTA in asymptomatic patients had a low diagnostic yield (9.3%) and a higher frequency of inappropriate or uncertain CAG (92.1%) and PCI (63.2%). The overt clinical benefit of coronary revascularization (ie, appropriate PCI or CABG) was observed in only 0.7% (165/23 335) of the overall asymptomatic patients. Considering the radiation hazard and potential complications related to CAG or PCI, the overall benefits of coronary CTA might not substantially overwhelm its potential risks; therefore, the low threshold for performing cardiac CT or coronary CTA in an asymptomatic and low-risk population cannot be readily justified. In this context, clinicians need to better adhere to the decision-making algorithms supported by established guidelines and the appropriate use criteria of coronary CTA.

In this contemporary clinical practice, the diagnostic yield of coronary CTA for revealing obstructive CAD was low. Specifically, <10% of patients without clinical symptoms had obstructive CAD. We also systematically assessed the appropriateness of the subsequent diagnostic-therapeutic procedures after coronary CTA. Among symptomatic patients, 19.2%, 9.9%, and 2.4% underwent subsequent CAG, PCI, and CABG, respectively, which were mostly deemed as appropriate

(80.6%, 61.5%, and 85.9%, respectively). However, only a minor portion of subsequent CAG and PCI procedures in asymptomatic patients were regarded as appropriate (7.9% and 38.0%, respectively). Not surprisingly, we found that the rate of obstructive CAD on CTA was proportionally higher in patients with high Framingham risk scores than in those with intermediate or low risk scores. These findings suggest that a more adequate pretest clinical assessment is required and that adherence to the current guideline for appropriate use of coronary CTA is the best way to encourage "appropriate" diagnostic-therapeutic cascades.

The main clinical reasons for performing coronary CTA are to more accurately detect or exclude significant CAD and eventually reduce long-term negative clinical outcomes, such as death or MI. A prior observational study showed that although CTA was associated with a higher rate of subsequent invasive cardiac procedures and higher CAD-related medical costs compared with stress testing, patients who underwent CTA had a similar risk of death and a slightly lower risk of MI-related hospitalization.[9] The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) showed that compared with functional testing, the strategy of initial CTA did not significantly improve the primary end point events over 2 years.[29] In contrast, the SCOT-HEART (Scottish Computed Tomography of the Heart) trial demonstrated that the use of CTA in addition to standard care in patients with stable chest pain resulted in a significantly lower rate of death from coronary
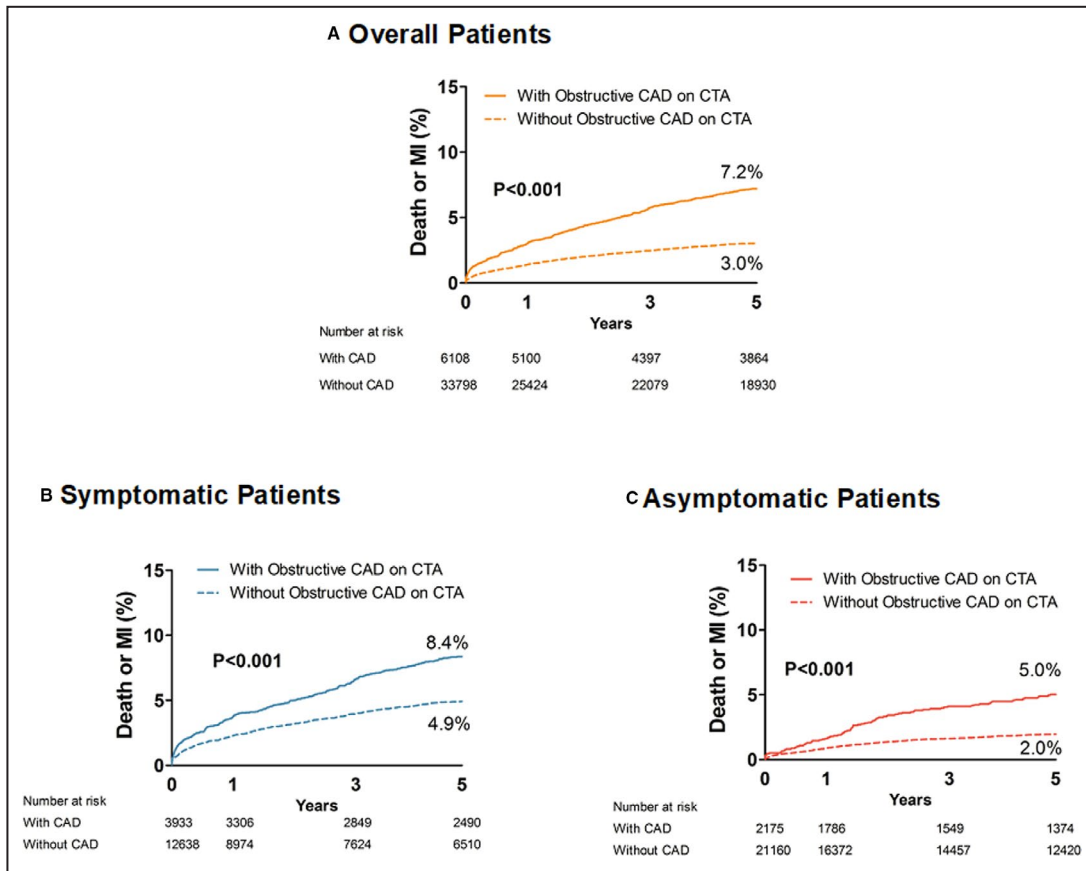
Figure 4. Kaplan-Meyer curves of the primary outcome of death or myocardial infarction (MI) according to the presence of obstructive coronary artery disease (CAD) on coronary computed tomographic angiography (CTA).
Obstructive CAD was defined as >50% stenosis in a major epicardial coronary artery on coronary CTA. Results are presented among the overall patients (**A**), symptomatic patients (**B**), and asymptomatic patients (**C**).

heart disease or MI at 5 years than standard care alone.[32] To better understand the relationship between the current decision-making processes for the need for coronary CTA and its clinical impact, we explored the relative usefulness of well-known risk scores, major cardiac risk factors, symptoms,

Table 4. Predictors of the 5-Year Primary Composite Outcomes of Death or MI

Variables	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Framingham risk score (vs low)				
Intermediate	1.55 (1.37–1.76)	<0.001	1.42 (1.25–1.61)	<0.001
High	2.90 (2.43–3.47)	<0.001	1.80 (1.49–2.17)	<0.001
Body mass index (vs normal)*				
Underweight (<18.5 kg/m^2)	2.71 (1.97–3.73)	<0.001	2.28 (1.61–3.07)	<0.001
Overweight (≥25.0 kg/m^2)	0.96 (0.85–1.09)	0.53	0.99 (0.87–1.12)	0.83
Diabetes mellitus	2.09 (1.85–2.35)	<0.001	1.64 (1.45–1.86)	<0.001
Cerebrovascular disease	1.72 (1.38–2.14)	<0.001	1.06 (0.85–1.33)	0.60
Estimated GFR <60 mL/min	3.37 (2.96–3.84)	<0.001	2.31 (2.01–2.65)	<0.001
Symptoms at coronary CTA	2.63 (2.33–2.96)	<0.001	2.09 (1.84–2.37)	<0.001
Obstructive CAD on coronary CTA	2.40 (2.12–2.71)	<0.001	1.34 (1.17–1.54)	<0.001

CAD indicates coronary artery disease; CTA, computed tomographic angiography; GFR, glomerular filtration rate; HR, hazard ratio; and MI, myocardial infarction.

*Body mass index was classified into 3 groups: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), and overweight (≥25.0 kg/m^2).
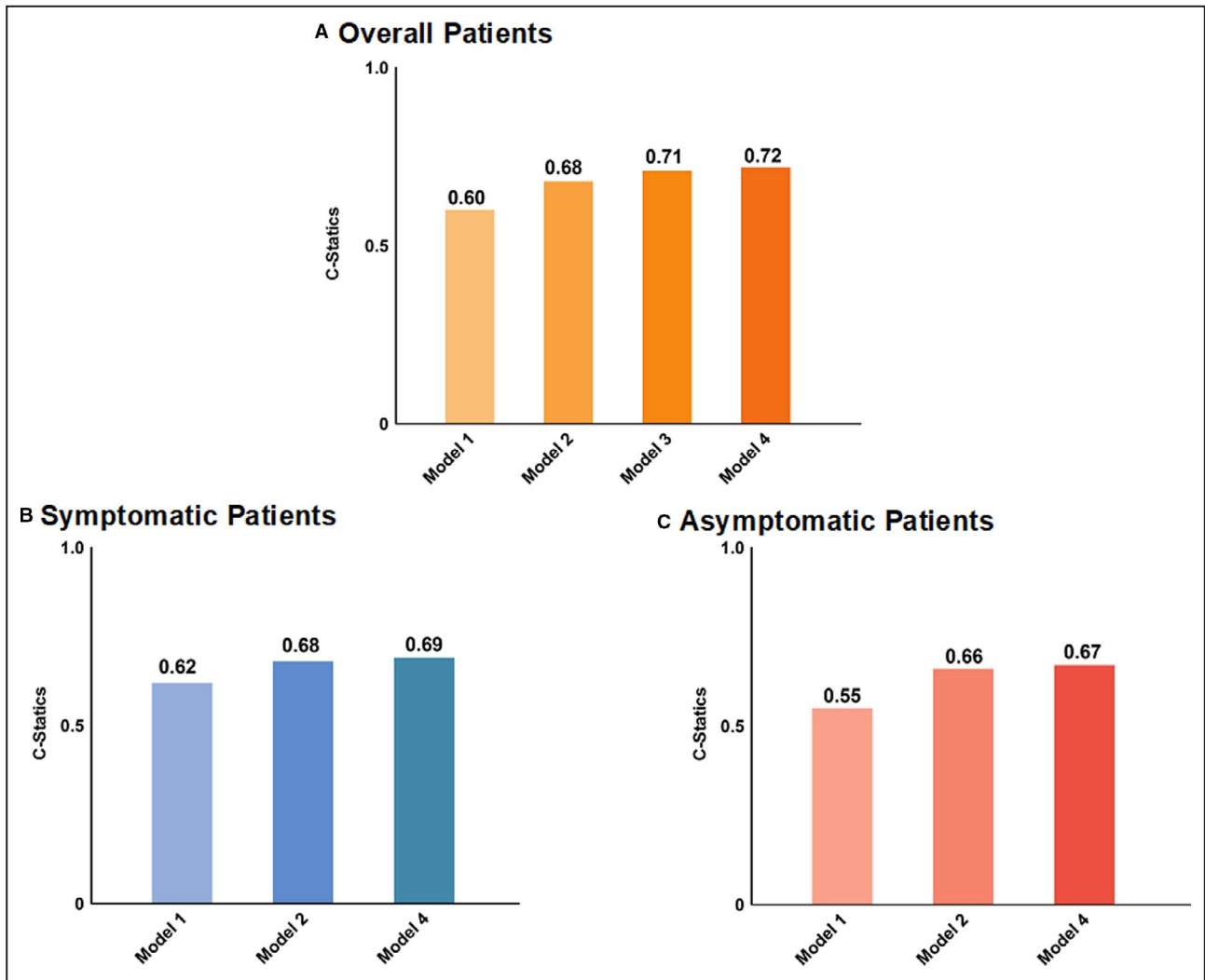
Figure 5. Predictive ability of information obtained from clinical risk assessment and coronary computed tomographic angiography (CTA) findings for the primary composite outcome of death or myocardial infarction at 5 years.
Model 1 included the Framingham risk score only. Clinical risk factors not included in the Framingham risk score (ie, diabetes mellitus, body mass index, baseline renal insufficiency [creatinine clearance <60 mL/min], and history of cerebrovascular disease) were added in model 2, symptoms in model 3, and the presence of obstructive coronary artery disease on CTA in model 4. Results are presented among the overall patients (**A**), symptomatic patients (**B**), and asymptomatic patients (**C**).

and CTA results for predicting the composite outcome of death or MI. Although the presence of CAD on CTA had a significant association with the occurrence of death or MI, the additional prognostic value of coronary CTA findings over the conventional clinical risk assessment was limited, increasing the C-statistic from 0.711 to 0.716. The predictability of future major cardiovascular events, as assessed before coronary CTA, was generally estimated by considering the traditional risk factors and the presence of symptoms. Our findings are in line with those of recent reports that routine CTA screening was not associated with better clinical outcomes in symptomatic subjects[29,33] or even high-risk diabetic patients.[34] These results emphasize the need for

further refinement of coronary CTA indications with a bayesian approach to maximize its clinical benefit over invasive tools or indirect functional testing in daily clinical practice.[35]

Our study has several limitations. First, this study was a nonrandomized observational cohort study. Therefore, the observed findings should be considered hypothesis generating. Second, because of the observational nature of the study, the exact reasons for the decision to proceed with coronary CTA are unclear. Third, to reduce ascertainment bias, we excluded patients with a known history of CAD. Therefore, our population mainly consisted of relatively healthy subjects and thus the number of clinical events was lower than those in prior studies.
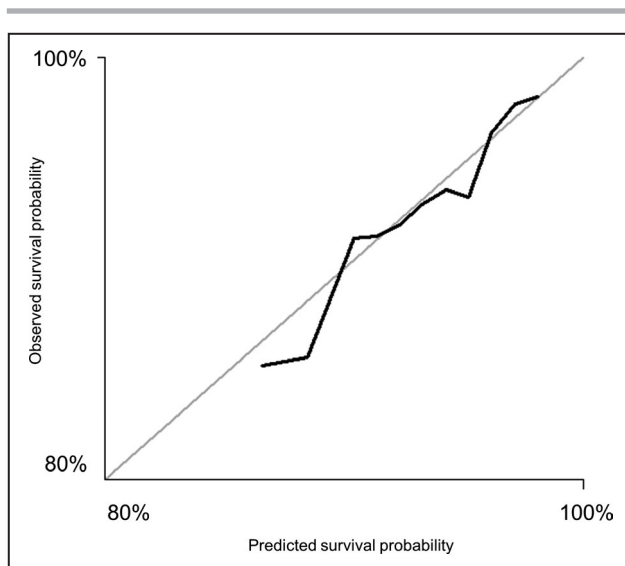
Figure 6. The calibration plot for the final model.
The calibration plot showed the agreement between predicted and observed survival rate.

clinical benefit of coronary CTA in contemporary clinical settings.

Fourth, in the present study, there was no comparator group (ie, functional or even no testing) as used in prior trials[29,32]; thus, the results cannot be considered clinically directive. Fifth, our study focused on stenosis and did not evaluate the status of nonobstructive plaques on CTA and its clinical impact. The most important mechanism of benefit of coronary CTA may be through the identification of obstructive or nonobstructive CAD, leading to the initiation of evidence-based preventative medical therapies.[36] Also, a previous study showed that nonobstructive CAD accounted for >50% of subsequent MI.[37] Last, given that the study population was relatively heterogeneous and included asymptomatic patients who were self-referred or tested for preoperative evaluation, the low diagnostic yield and limited prognostic value of CTA might lack external validity and therefore must be interpreted in the context of the population studied.

CONCLUSIONS

In this contemporary clinical-practice study, the number of coronary CTAs had substantially increased over time. However, the diagnostic yield of coronary CTA for obstructive CAD was low. The incremental use of coronary CTA in asymptomatic patients had led to increases in the rates of inappropriate diagnostic or therapeutic procedures without a substantial improvement in the prediction for death or MI. The decision-making for performing coronary CTA, including assessment of clinical factors and symptoms, needs to be substantially improved to increase the diagnostic yield and

REFERENCES

1. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–e164.
2. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949–3003.
3. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359:2324–2336.
4. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA, Nieman K, van Werkhoven JM, Pundziute G, Weustink AC, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol*. 2008;52:2135–2144.
5. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895.
6. Dreisbach JG, Nicol ED, Roobottom CA, Padley S, Roditi G. Challenges in delivering computed tomography coronary angiography as the first-line test for stable chest pain. *Heart*. 2018;104:921–927.
7. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477.
8. Einstein AJ. Effects of radiation exposure from cardiac imaging: how good are the data? *J Am Coll Cardiol*. 2012;59:553–565.
9. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. *JAMA*. 2011;306:2128–2136.
10. Kang SH, Park GM, Lee SW, Yun SC, Kim YH, Cho YR, Park HW, Suh J, Yang DH, Kang JW, et al. Long-term prognostic value of coronary

CT angiography in asymptomatic type 2 diabetes mellitus. *JACC Cardiovasc Imaging*. 2016;9:1292–1300.

11. Yang DH, Kang J-W, Kim H-K, Choe J, Baek S, Kim SH, Park G-M, Kim Y-H, Kim TH, Tseng W-YI. Association between C-reactive protein and type of coronary arterial plaque in asymptomatic patients: assessment with coronary CT angiography. *Radiology*. 2014;272:665–673.

12. Hausleiter J, Meyer T, Hadamitzky M, Kastrati A, Martinoff S, Schomig A. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. *J Am Coll Cardiol*. 2006;48:312–318.

13. Patel MR, Bailey SR, Bonow RO, Chambers CE, Chan PS, Dehmer GJ, Kirtane AJ, Wann LS, Ward RP. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: a report of the American College of Cardiology Foundation appropriate use criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;59:1995–2027.

14. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation appropriate use criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol*. 2012;59:857–881.

15. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020–2035.

16. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.

17. Larson DB, Johnson LW, Schnell BM, Salisbury SR, Forman HP. National trends in CT use in the emergency department: 1995–2007. *Radiology*. 2011;258:164–173.

18. Stocker TJ, Deseive S, Leipsic J, Hadamitzky M, Chen MY, Rubinshtein R, Heckner M, Bax JJ, Fang X-M, Grove EL. Reduction in radiation exposure in cardiovascular computed tomography imaging: results from the prospective multicenter registry on radiation dose estimates of cardiac CT angiography in daily practice in 2017 (PROTECTION VI). *Eur Heart J*. 2018;39:3715–3723.

19. Richards CE, Obaid DR. Low-dose radiation advances in coronary computed tomography angiography in the diagnosis of coronary artery disease. *Curr Cardiol Rev*. 2019;15:304–315.

20. Kim J, Goo BS, Cho Y-S, Youn T-J, Choi DJ, Dhanantwari A, Vembar M, Chun EJ. Diagnostic performance and image quality of iterative model-based reconstruction of coronary CT angiography using 100 kVp for heavily calcified coronary vessels. *PLoS One*. 2019;14:e0222315.

21. Hoffmann U, Bamberg F, Chae CU, Nichols JH, Rogers IS, Seneviratne SK, Truong QA, Cury RC, Abbara S, Shapiro MD, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (rule out myocardial infarction using computer assisted tomography) trial. *J Am Coll Cardiol*. 2009;53:1642–1650.

22. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, Rubin GD. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: a report of the American College of Cardiology Foundation appropriate use criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions,

23. An J, Shim JH, Kim SO, Lee D, Kim KM, Lim YS, Lee HC, Chung YH, Lee YS. Prevalence and prediction of coronary artery disease in patients with liver cirrhosis: a registry-based matched case-control study. *Circulation*. 2014;130:1353–1362.

24. Park GM, Kim SH, Jo MW, Her SH, Han S, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YH, et al. Clinical impact and cost-effectiveness of coronary computed tomography angiography or exercise electrocardiogram in individuals without known cardiovascular disease. *Medicine (Baltimore)*. 2015;94:e917.

25. Inohara T, Kohsaka S, Miyata H, Ueda I, Ishikawa S, Ohki T, Nishi Y, Hayashida K, Maekawa Y, Kawamura A, et al. Appropriateness ratings of percutaneous coronary intervention in Japan and its association with the trend of noninvasive testing. *JACC Cardiovasc Interv*. 2014;7:1000–1009.

26. Min JK, Labounty TM, Gomez MJ, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Cheng VC, et al. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. *Atherosclerosis*. 2014;232:298–304.

27. Halon DA, Azencot M, Rubinshtein R, Zafrir B, Flugelman MY, Lewis BS. Coronary computed tomography (CT) angiography as a predictor of cardiac and noncardiac vascular events in asymptomatic type 2 diabetics: a 7-year population-based cohort study. *J Am Heart Assoc*. 2016;5:e003226. DOI: 10.1161/JAHA.116.003226.

28. Hadamitzky M, Achenbach S, Al-Mallah M, Berman D, Budoff M, Cademartiri F, Callister T, Chang HJ, Cheng V, Chinnaiyan K, et al. Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry). *J Am Coll Cardiol*. 2013;62:468–476.

29. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372:1291–1300.

30. Bekwelem W, Connolly SJ, Halperin JL, Adabag S, Duval S, Chrolavicius S, Pogue J, Ezekowitz MD, Eikelboom JW, Wallentin LG, et al. Extracranial systemic embolic events in patients with nonvalvular atrial fibrillation: incidence, risk factors, and outcomes. *Circulation*. 2015;132:796–803.

31. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"—screening and overdiagnosis. *N Engl J Med*. 2014;371:1765–1767.

32. Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, Flather M, Forbes J, Hunter A, Lewis S, MacLean S, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379:924–933.

33. The SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. 2015;385:2383–2391.

34. Muhlestein JB, Lappé DL, Lima JA, Rosen BD, May HT, Knight S, Bluemke DA, Towner SR, Le V, Bair TL. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the factor-64 randomized clinical trial. *JAMA*. 2014;312:2234–2243.

35. Bittencourt MS, Hulten EA, Veeranna V, Blankstein R. Coronary computed tomography angiography in the evaluation of chest pain of suspected cardiac origin. *Circulation*. 2016;133:1963–1968.

36. Adamson PD, Williams MC, Dweck MR, Mills NL, Boon NA, Daghem M, Bing R, Moss AJ, Mangion K, Flather M, et al. Guiding therapy by coronary CT angiography improves outcomes in patients with stable chest pain. *J Am Coll Cardiol*. 2019;74:2058–2070.

37. Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR, Huang M, Pencina M, Mark DB, Heitner JF, et al. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (prospective multicenter imaging study for evaluation of chest pain). *Circulation*. 2017;135:2320–2332.