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ORIGINAL RESEARCH

Cardiovascular Outcomes of Coronary Computed Tomography Angiography Versus Functional Testing in Suspected Coronary Syndromes: Real-World Evidence From the Nationwide Cohort

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BACKGROUND: Real-world evidence for the selection of gatekeeping studies in patients with suspected coronary syndromes is limited.

METHODS AND RESULTS: We identified 27 036 patients who underwent coronary computed tomography angiography (CCTA), single-photon emission computed tomography, and the treadmill test for suspected coronary syndromes from the Korean National Health Insurance Service–National Sample Cohort between 2006 and 2014. The primary end point was a composite of cardiac death and myocardial infarction, and the secondary end point was a composite of the primary end point and revascularization. During a median follow-up of 5.4 years, the risk of both primary and secondary end points was significantly higher in the single-photon emission computed tomography group (hazard ratio [HR], 1.81 [95% CI, 1.34–2.45]; and HR, 1.42 [95% CI, 1.22–1.66]), but significantly lower in the treadmill test group (HR, 0.53 [95% CI, 0.42–0.67]; and HR, 0.69 [95% CI, 0.62–0.76]) compared with the CCTA group. After balancing baseline risk factors, there was no significant difference in the primary end point in those with single-photon emission computed tomography (HR, 1.11 [95% CI, 0.78–1.57]; P=0.58) or treadmill test (HR, 0.84 [95% CI, 0.65–1.08]; P=0.18) groups, compared with the CCTA group. The event rate of the secondary end point was significantly lower in the treadmill test group than in the CCTA group (HR, 0.87 [95% CI, 0.78–0.96]; P=0.008).

CONCLUSIONS: Compared with functional testing, initial CCTA was not associated with a lower rate of cardiac death or myocardial infarction when used as an initial diagnostic test for patients with suspected coronary syndromes.

Key Words: chronic coronary syndromes ■ coronary computed tomography angiography ■ functional testing

See Editorial by Mancini

Given the wide array of possible etiologies, patients with chest pain present a diagnostic challenge.[1] Coronary artery disease (CAD) is one of the most common causes of chest pain, and its prevalence has been gradually increasing, reaching 1655 per 100 000 people in 2017.[2] Invasive coronary angiography is the gold standard for CAD diagnosis and is often followed by coronary revascularization procedures. However, given

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CLINICAL PERSPECTIVE

What Is New?

- This nationwide cohort study of 27 036 patients with suspected coronary syndromes demonstrated that the primary composite outcome (cardiac death, myocardial infarction) was higher for patients undergoing single-photon emission computed tomography and lower for the treadmill test compared with coronary computed tomography angiography as an initial investigation.
- After adjustment for baseline risk factors, initial coronary computed tomography angiography for suspected coronary syndromes was not associated with a reduction of cardiac death and myocardial infarction compared with functional testing groups nor with augmented use of preventive medications.

What Are the Clinical Implications?

- Our findings suggest that CCTA is not superior for suspected coronary syndromes in reduction of cardiovascular outcomes compared with functional testing.
- Gatekeeping studies for suspected coronary syndromes should be selected on the basis of the patient characteristics in clinical practice.

Nonstandard Abbreviations and Acronyms

CONSERVE	Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization
IPTW	inverse probability of treatment weighting
PRECISE	Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization
PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
SCOT-HEART	Scottish Computed Tomography of the Heart

the invasiveness and potential risks of invasive coronary angiography and the low diagnostic yield of elective invasive coronary angiography for suspected CAD, noninvasive tests are generally recommended as an initial investigation in patients who do not have a high clinical likelihood of CAD.[3–5]

The selection of the initial noninvasive modality among various functional and anatomic studies is another challenging issue in clinical practice, and strategies for patient management vary according to the results of the initial test. Traditionally, functional tests, such as the treadmill test (TMT) and stress nuclear single-photon emission computed tomography (SPECT), have been reported to provide excellent prognostic value for cardiovascular events.[6–8] With advances in computed tomography techniques, sequential studies have also proven that coronary computed tomography angiography (CCTA) is not only predictive of future cardiovascular events, but also highly sensitive for detecting the absence of CAD.[9,10]

Large randomized controlled trials have been conducted to compare the efficacy of anatomic and functional testing in patients with suspected coronary syndromes.[11,12] The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial showed that the rate of major adverse cardiovascular events did not significantly differ between CCTA and functional stress testing.[11] In the SCOT-HEART (Scottish Computed Tomography of the Heart) trial, the use of CCTA in addition to standard care in patients with stable chest pain was associated with a reduction of the rate of death from coronary heart disease or nonfatal myocardial infarction (MI) and augmented use of preventive medications.[12] Given the heterogeneity in the clinical efficacy of functional testing and CCTA in clinical trials, the use of CCTA as a first-line noninvasive imaging modality above functional testing in patients with stable chest pain is still controversial. More importantly, despite the vast volume of clinical studies, real-world data comparing the cardiovascular outcomes of gatekeeping studies in patients with suspected coronary syndromes are limited.

Thus, we sought to compare the clinical outcomes of noninvasive gatekeeping studies in patients with suspected coronary syndromes using the nationwide claims database of the National Health Insurance Service in South Korea.

METHODS

This study was approved by the institutional review board (2103–003-19 357), and the requirement for written informed consent was waived because all personal data were removed and coded as arbitrary numbers.

Data can be accessed through the National Health Insurance Data Sharing Service website (http://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do). A completed application form, a research proposal, and the institutional review board approval document should be submitted to the Review Committee of Research Support in the Korean National Health Insurance Service to gain access to data.

Data Source

The Korean National Health Insurance Service–National Sample Cohort database from 2006 to 2014 was used. The National Health Insurance Service–National Sample Cohort is a representative sample cohort of 1 million subjects randomly selected from all beneficiaries of the National Health Insurance and National Medical Aid in 2006.[13] The database includes personal and medical information such as age, sex, diagnosis, and surgical or medical treatment. The diagnoses were coded according to the *International Classification of Diseases*, *Tenth Revision* (*ICD-10*).

Study Population

From the National Health Insurance Service–National Sample Cohort database between 2006 and 2014, we identified 29 835 patients who underwent 1 of the noninvasive diagnostic strategies including CCTA (HA474), TMT (E6543), and SPECT (HC292, HC297, HC298, HC301, HC302, HC303, HC304, HC305) under clinical diagnoses of angina pectoris (I20), other symptoms and signs involving the circulatory and respiratory systems (R09), pain in the throat and chest (R07), atherosclerosis (I70), and abnormalities of breathing (R06) as a primary diagnosis in an outpatient clinical setting. Patients who underwent noninvasive diagnostic tests for suspected coronary syndromes multiple times were categorized on the basis of the results of their initial test. Among them, we excluded patients who underwent revascularization, including percutaneous coronary intervention (M6561, M6562, M6563, M6564, M6565, M6566, and M6567) or coronary artery bypass grafting (O1640, O1641, O1642, O1647, O1648, O1649, OA640, OA641, OA642, OA647, OA648, and OA649) or had MI (I21) at any time before the index test. Patients who died during the test month were excluded from the study. Ultimately, 27 036 patients were included in this study (Figure 1). Baseline information, including age, sex, and medication, was obtained, and comorbid conditions were assessed.

Study End Point

The primary end point was a composite of cardiac death and MI during the follow-up period. The secondary end point was the composite of the primary end point and revascularization. Change of medical treatments after the index test was also analyzed. Medication changes were defined as changes in the use of a drug within 90 days following the index test. Table S1 summarizes the *ICD-10* codes for the study end points.

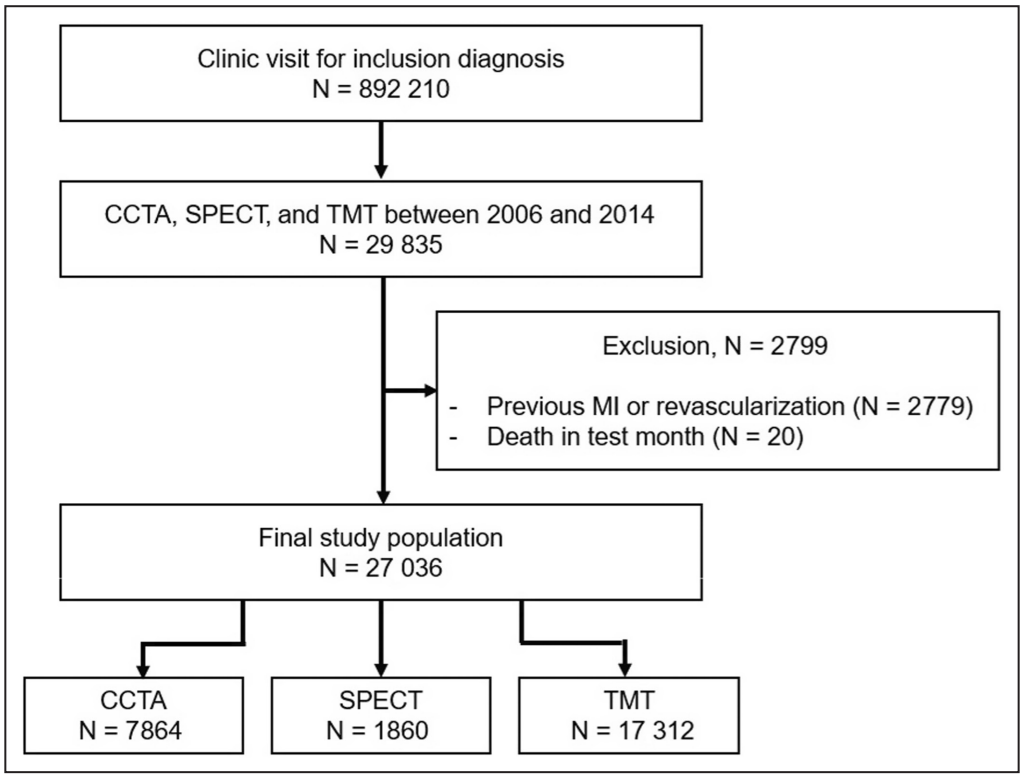

Figure 1. Identification of the study population.
CCTA indicates coronary computed tomography angiography; MI, myocardial infarction; SPECT, single-photon emission computed tomography; and TMT, treadmill test.

Statistical Analysis

Categorical variables are presented as percentages, and continuous variables are described as means with SDs. To examine differences among study groups, we used the analysis of variance test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. The Cox proportional-hazards model was used to estimate hazard ratios (HRs) with 95% CIs for cardiac death, MI, revascularization. Inverse probability of treatment weighting (IPTW) was used to balance patient characteristics among the study groups. The covariates included in the IPTW were age, sex, comorbidities, and previous aspirin use. Cumulative event rates were calculated for each group as a function of time from the index test date using the Kaplan–Meier method. Statistical analyses were performed using R version 3.3.2 (R Foundation, www.R-project.org), and the twang package was used for IPTW among the study groups. A *P* value of <0.05 was considered statistically significant, and a *P* value of <0.017 was considered to indicate statistical significance in pairwise comparison (accounting for a Bonferroni correction).

RESULTS

Baseline Characteristics

The baseline characteristics of patients who underwent CCTA (n=7864), SPECT (n=1860), and TMT (n=17 312) as first-line diagnostic modalities are summarized in Table 1. The distribution of patient age, sex, and risk factors differed significantly among the study groups: The mean age of the patients in the TMT group (51.8±13.9) was significantly lower than that in the CCTA (57.7±14.5) and SPECT (62.4±11.8) groups (*P*<0.001); SPECT was performed more frequently in female patients (53.6%) than CCTA (47.5%) and TMT (46.6%) (*P*<0.001); and the mean Charlson Comorbidity Index of patients who underwent SPECT (4.28±2.99) was significantly higher than that of patients who underwent TMT (2.72±2.37) or CCTA (3.58±2.91) (*P*<0.001).

Clinical Outcomes

Table 2 summarizes the unadjusted outcomes according to gatekeeper groups. The median follow-up period was 5.4 years (interquartile range, 3.2–7.5 years). During the follow-up period, 126 patients (1.6%) in the CCTA group, 63 patients (3.4%) in the SPECT group, and 160 patients (0.9%) in the TMT group had a primary end point event. Compared with the CCTA group, the composite rate of cardiac death and MI was significantly higher in the SPECT group (HR, 1.81 [95% CI, 1.34–2.45]; *P*<0.001) but significantly lower in the TMT group (HR, 0.53 [95% CI, 0.42–0.67]; *P*<0.001). Similarly, the occurrence rate of secondary end point, composite of cardiac death, MI, and revascularization, was higher in the SPECT group (HR, 1.42 [95% CI, 1.22–1.66]; *P*<0.001) but lower in the TMT group (HR, 0.69 [95% CI, 0.62–0.76]; *P*<0.001) compared with the CCTA group.

After adjusting for baseline risk factors using IPTW, the weighted baseline characteristics were well balanced for all variables (Table S2). Table 3 and Figure 2 present the outcomes after adjustment. The risk of the primary end point did not differ significantly after adjustment between those who underwent CCTA and SPECT (IPTW HR, 1.11 [95% CI, 0.78–1.57]; *P*=0.58). Although the rate of cardiac death was significantly lower in the TMT group than in the CCTA group after adjustment (IPTW HR, 0.64 [95% CI, 0.44–0.92]; *P*=0.016), the composite event rates of cardiac death and MI did not differ significantly between the TMT and CCTA groups (IPTW HR, 0.84 [95% CI, 0.65–1.08]; *P*=0.18).

For the secondary end point, composite of cardiac death, MI, and revascularization, no significant difference was observed between those who underwent CCTA and SPECT (IPTW HR, 1.08 [95% CI, 0.88–1.31]; *P*=0.47). However, the secondary end point event rate in patients who underwent TMT was significantly lower than that in the CCTA group (IPTW HR, 0.87 [95% CI, 0.78–0.96]; *P*=0.008).

Medication Changes

Table 4 summarizes the change of medication use before and after the index tests. The proportion of medication change differed significantly according to initial diagnostic test for aspirin, clopidogrel, and statin. After adjustment using IPTW, use of aspirin and clopidogrel was less frequently changed in the CCTA group compared with functional testing groups (Table 5). Initiation of antiplatelet agents was more frequently observed in functional testing groups compared with the CCTA group (Table S3). Statin therapy was more frequently changed in the SPECT group and the TMT group compared with CCTA group (20.5% versus 19.5%, *P*=0.008; and 21.0% versus 19.5%, *P*<0.001) (Table 5). Also, initiation of statin therapy was more frequently observed in functional testing groups compared with the CCTA group (Table S3).

DISCUSSION

Our study compared cardiovascular outcomes between patients who underwent CCTA and noninvasive functional tests as gatekeepers for suspected coronary syndromes using longitudinal data from a national sample cohort with a 5.4-year follow-up period.

Table 1. Baseline Characteristics According to the Initial Investigation Modality

Characteristics	CCTA (n=7864)	SPECT (n=1860)	TMT (n=17 312)	*P* value	*P* value on pairwise comparison		
					CCTA vs SPECT	SPECT vs TMT	CCTA vs TMT
Age, y	57.8±14.5	62.4±11.8	51.8±13.9	<0.001	<0.001	<0.001	<0.001
Female sex, n (%)	3733 (47.5)	997 (53.6)	8073 (46.6)	<0.001	<0.001	<0.001	0.22
Comorbid conditions							
Hypertension, n (%)	4330 (55.1)	1335 (71.8)	8279 (47.8)	<0.001	<0.001	<0.001	<0.001
Hyperlipidemia, n (%)	4394 (55.9)	1303 (70.1)	9168 (53.0)	<0.001	<0.001	<0.001	<0.001
Diabetes, n (%)	3349 (42.6)	1074 (57.7)	6306 (36.4)	<0.001	<0.001	<0.001	<0.001
Heart failure, n (%)	631 (8.0)	225 (12.1)	887 (5.1)	<0.001	<0.001	<0.001	<0.001
Chronic kidney disease, n (%)	185 (2.4)	130 (7.0)	330 (1.9)	<0.001	<0.001	<0.001	0.02
Atrial fibrillation, n (%)	361 (4.6)	149 (8.0)	669 (3.9)	<0.001	<0.001	<0.001	0.008
Hemorrhagic stroke, n (%)	144 (1.8)	46 (2.5)	180 (1.0)	<0.001	0.09	<0.001	<0.001
Ischemic stroke, n (%)	970 (12.3)	304 (16.3)	1191 (6.9)	<0.001	<0.001	<0.001	<0.001
Peripheral arterial occlusive disease, n (%)	784 (10.0)	232 (12.5)	1193 (6.9)	<0.001	0.002	<0.001	<0.001
Previous aspirin use, n (%)	2938 (37.4)	942 (50.6)	5559 (32.1)	<0.001	<0.001	<0.001	<0.001
Previous clopidogrel use, n (%)	551 (7.0)	176 (9.5)	810 (4.7)	<0.001	<0.001	<0.001	<0.001
Previous statin use, n (%)	2307 (29.3)	744 (40.0)	4474 (25.8)	<0.001	<0.001	<0.001	<0.001
Previous ACE inhibitor use, n (%)	1006 (12.8)	394 (21.2)	1687 (9.7)	<0.001	<0.001	<0.001	<0.001
Previous ARB use, n (%)	2239 (28.5)	715 (38.4)	3984 (23.0)	<0.001	<0.001	<0.001	<0.001
Previous beta blocker use, n (%)	2503 (31.8)	759 (40.8)	4779 (27.6)	<0.001	<0.001	<0.001	<0.001
Charlson Comorbidity Index, mean	3.58±2.91	4.28±2.99	2.72±2.37	<0.001	<0.001	<0.001	<0.001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCTA, coronary computed tomography angiography; SPECT, single-photon emission computed tomography; and TMT, treadmill test.

Compared with functional stress tests, CCTA was not associated with a reduction in the primary composite outcome of cardiac death or MI when used as a gatekeeper.

Various studies have compared the clinical efficacy of CCTA with that of functional studies for suspected coronary syndromes. In the PROMISE trial, 10 003 patients were randomly assigned to CCTA or functional testing for suspected CAD. Compared with functional testing, initial CCTA did not improve clinical outcomes over a median follow-up of 2 years.[11] In the SCOT-HEART trial, which enrolled 4146 patients with stable chest pain who underwent a routine clinical evaluation including exercise electrocardiography, there was a significant reduction in the rate of death from coronary heart disease or nonfatal MI in the standard care plus CCTA group compared with the standard care group during a median follow-up of 4.8 years.[12] In a Danish nationwide registry study with a median follow-up of 3.6 years, CCTA was associated with a lower risk of MI, but a similar risk of all-cause death, compared with functional tests as an initial investigation modality for CAD.[14] Due to these heterogeneous study settings and results, selection of the optimal initial diagnostic modality for the evaluation of suspected coronary syndromes still requires more evidence. Fortunately, the results of the PRECISE (Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and

Table 2. Unadjusted Outcomes According to the Initial Diagnostic Test

End points	CCTA (n=7864)	SPECT (n=1860)	TMT (n=17 312)	Unadjusted HR (95% CI) SPECT (vs CCTA)	Unadjusted HR (95% CI) TMT (vs CCTA)
Primary composite end point, n (%)	126 (1.6)	63 (3.4)	160 (0.9)	1.81 (1.34–2.45, *P*<0.001)	0.53 (0.42–0.67, *P*<0.001)
Cardiac death	79 (1.0)	30 (1.6)	62 (0.4)		
Myocardial infarction	53 (0.7)	34 (1.8)	104 (0.6)		
Primary end point plus revascularization, n (%)	617 (7.8)	220 (11.8)	976 (5.6)	1.42 (1.22–1.66, *P*<0.001)	0.69 (0.62–0.76, *P*<0.001)
Revascularization	553 (7.0)	194 (10.4)	929 (5.4)		

CCTA indicates coronary computed tomography angiography; HR, hazard ratio; SPECT, single-photon emission computed tomography; and TMT, treadmill test.

Table 3. Adjusted Outcomes According to the Initial Diagnostic Test After IPTW

End points	IPTW HR (95% CI) SPECT (vs CCTA)	IPTW HR (95% CI) TMT (vs CCTA)
Primary composite end point	1.11 (0.78–1.57, *P*=0.58)	0.84 (0.65–1.08, *P*=0.18)
Cardiac death	0.91 (0.55–1.48, *P*=0.69)	0.64 (0.44–0.92, *P*=0.02)
Myocardial infarction	1.24 (0.77–2.02, *P*=0.38)	1.04 (0.74–1.48, *P*=0.81)
Primary end point plus revascularization	1.08 (0.88–1.31, *P*=0.47)	0.87 (0.78–0.96, *P*=0.008)
Revascularization	1.09 (0.88–1.34, *P*=0.43)	0.89 (0.80–1.00, *P*=0.05)

CCTA indicates coronary computed tomography angiography; HR, hazard ratio; IPTW, inverse probability of treatment weighting; SPECT, single-photon emission computed tomography; and TMT, treadmill test.

Revascularization) trial is upcoming, in which 2103 patients with stable chest pain were enrolled and randomly assigned to a precision strategy group or usual care.[15] The study might provide strong evidence for the optimal evaluation strategy for patients with stable chest pain.[15] One major limitation of contemporary clinical trials was that they were conducted in the Western countries, and large-scale studies for Asian populations are scarce. Our study provides evidence for the selection of gatekeepers on the basis of real-world

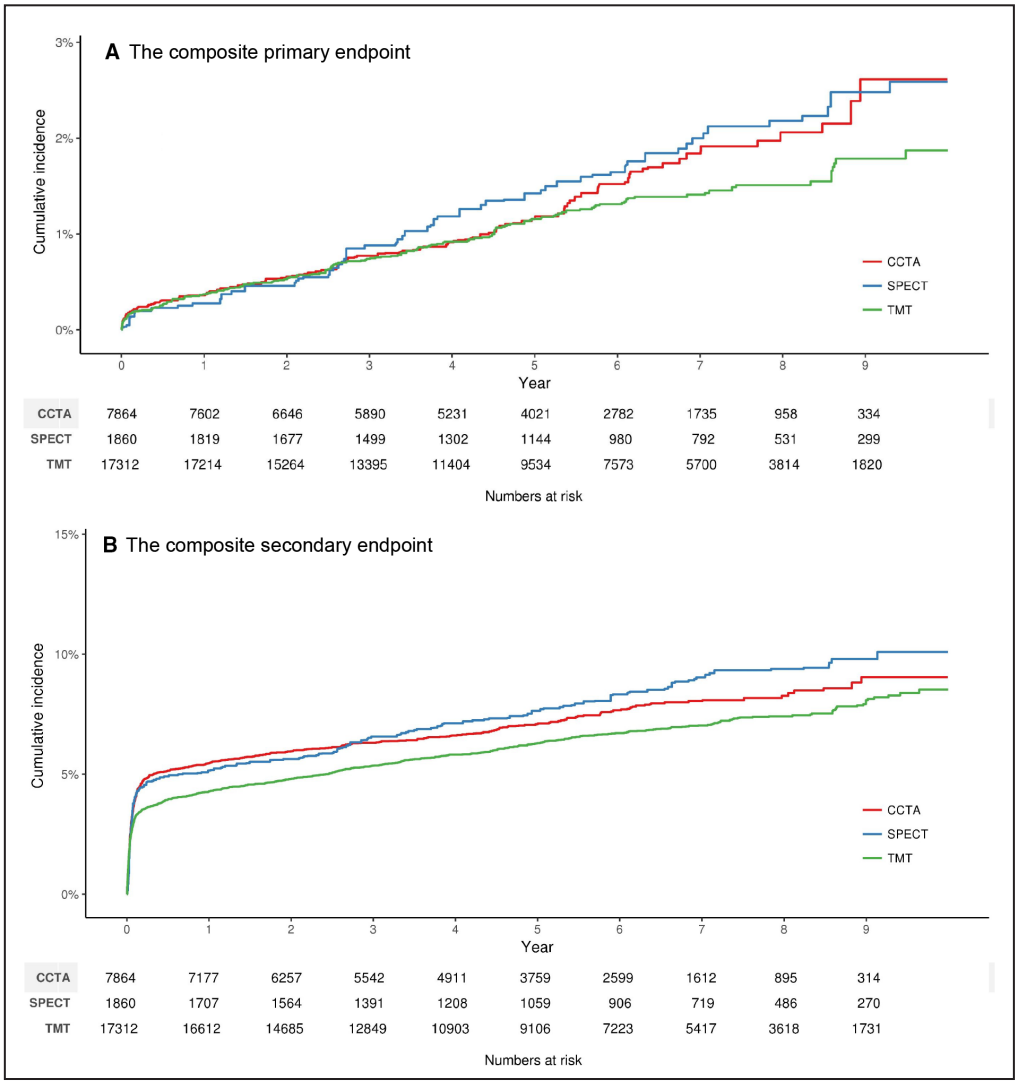

Figure 2. Adjusted Kaplan–Meier estimates of end points.
Adjusted Kaplan-Meier estimates of the composite primary end point (**A**) and the composite secondary endpoint (**B**) according to initial noninvasive testing. CCTA indicates coronary computed tomography angiography; SPECT, single-photon emission computed tomography; and TMT, treadmill test.

Table 4. Unadjusted Medication Changes Within 90 Days

		Medication before and after testing				Medication change	
		Initiated, n (%)	Continued, n (%)	Discontinued, n (%)	None, n (%)	Proportion, n (%)	*P* value
Aspirin	CCTA	597 (7.6)	1528 (19.4)	1410 (17.9)	4329 (55.0)	2007 (25.5)	CCTA vs SPECT *P*<0.001 CCTA vs TMT *P*=0.11
	SPECT	193 (10.4)	552 (29.7)	390 (21.0)	725 (39.0)	583 (31.3)	
	TMT	1759 (10.2)	2934 (16.9)	2625 (15.2)	9994 (57.7)	4384 (25.3)	
Clopidogrel	CCTA	516 (6.6)	262 (3.3)	289 (3.7)	6797 (86.4)	805 (10.2)	CCTA vs SPECT *P*<0.001 CCTA vs TMT *P*<0.001
	SPECT	156 (8.4)	76 (4.1)	100 (5.4)	1528 (82.2)	256 (13.8)	
	TMT	1108 (6.4)	375 (2.2)	435 (2.5)	15394 (88.9)	1543 (9.0)	
Statin	CCTA	696 (8.9)	1395 (17.7)	912 (11.6)	4861 (61.8)	1608 (20.4)	CCTA vs SPECT *P*<0.001 CCTA vs TMT *P*=0.92
	SPECT	182 (9.8)	463 (24.9)	281 (15.1)	934 (50.2)	463 (24.9)	
	TMT	1682 (9.7)	2707 (15.6)	1767 (10.2)	11156 (64.4)	3549 (20.5)	

CCTA indicates coronary computed tomography angiography; SPECT, single-photon emission computed tomography; and TMT, treadmill test.

data from the Korean population, including >27 000 patients with about 5-year median follow-up period.

The overall rate of cardiac death was 0.6% in our cohort, which is comparable with that in the SCOT-HEART trial (0.4%). Interestingly, however, the incidence of MI was 0.7% in our study, which was relatively lower than those of previous reports, such as in the Danish registry (1.3%) and SCOT-HEART trial (2.8%), despite a longer follow-up period. One possible explanation could be the different ethnicities among the studies. Our study population was composed of Asian patients, in whom the MI incidence is reported to be lower than that of the White population.[16] Indeed, the MI rate was also substantially low at 0.3% in the CONSERVE (Coronary Computed Tomographic Angiography for Selective Cardiac Catheterization) trial, in which >85% of participants were Asian.[17] Our results raise concerns regarding the universal application of major clinical trials and guidelines in patients with suspected coronary syndromes. Interethnic or international differences in the occurrence of cardiovascular events should be considered, and a more population-based approach is necessary in patients with stable chest pain.

In our study, there was a fundamental difference in the baseline characteristics among patients who underwent CCTA, SPECT, and the TMT. Patients in the SPECT group were older and had more comorbidities, whereas those in the TMT group were younger and had fewer comorbidities. These differences might arise from the patients' capacity to complete the study successfully. Indeed, low exercise capacity and baseline electrocardiographic abnormalities may reduce the diagnostic sensitivity and specificity of the TMT.[18] In addition, the contrast materials used in CCTA may cause kidney injury and heart rhythm variability, and severe coronary calcification can degrade computed tomography image interpretation.[19,20] Thus, test selection should be influenced by clinical judgment that takes into account these diverse patient characteristics. The effect size of patient-related factors might be larger than that of gatekeeper-related factors. Consequently, differences in the baseline characteristics among the

Table 5. Adjusted Medication Changes Within 90 Days After IPTW

		Medication before and after testing				Medication change	
		Initiated, n (%)	Continued, n (%)	Discontinued, n (%)	None, n (%)	Proportion, n (%)	*P* value
Aspirin	CCTA	1981 (7.5)	4767 (17.9)	4493 (16.9)	15330 (57.7)	6474 (24.4)	CCTA vs SPECT *P*<0.001 CCTA vs TMT *P*<0.001
	SPECT	2931 (11.7)	4957 (19.9)	3763 (15.1)	13316 (53.3)	6694 (26.8)	
	TMT	2797 (10.4)	5099 (19.0)	4267 (15.9)	14661 (54.7)	7064 (26.3)	
Clopidogrel	CCTA	1641 (6.2)	689 (2.6)	821 (3.1)	23421 (88.1)	2462 (9.3)	CCTA vs SPECT *P*=0.006 CCTA vs TMT *P*=0.01
	SPECT	1701 (6.8)	693 (2.8)	789 (3.2)	21785 (87.3)	2490 (10.0)	
	TMT	1857 (6.9)	746 (2.8)	804 (3.0)	23417 (87.3)	2661 (9.9)	
Statin	CCTA	2299 (8.7)	4452 (16.8)	2894 (10.9)	16927 (63.7)	5193 (19.5)	CCTA vs SPECT *P*=0.008 CCTA vs TMT *P*<0.001
	SPECT	2397 (9.6)	4465 (17.9)	2716 (10.9)	15390 (61.6)	5113 (20.5)	
	TMT	2729 (10.2)	4601 (17.2)	2910 (10.8)	16585 (61.8)	5639 (21.0)	

CCTA indicates coronary computed tomography angiography; IPTW, inverse probability treatment weighting; SPECT, single-photon emission computed tomography; and TMT, treadmill test.

study groups may result in different cardiovascular outcomes.

We used IPTW to balance the baseline characteristics of the study groups. After adjustment, there was no difference in the primary composite end points of cardiac death and MI between CCTA and functional studies. Interestingly, a reduction in secondary composite outcomes, including cardiac death, MI, and revascularization, was observed in patients who underwent TMT rather than CCTA as a gatekeeper. In addition, the use of CCTA was not associated with increased medical treatments, including statin and antiplatelet agents, compared with functional testing groups, unlike previous trials such as SCOT-HEART and PRECISE. Our results suggest that CCTA testing, in both adjusted and unadjusted analyses, is not associated with superior use of preventive medications such as statin and antiplatelet agents. The converse in other studies has been used to explain the association of CCTA testing with reduced future cardiovascular events. In this real-world study, patients undergoing CCTA testing had a trend toward fewer initiations of such medications. This may contribute to the lack of CCTA-associated reduction in events in this real-world analysis. Thus, indiscriminate use of CCTA as a gatekeeper for every patient with chest pain should be avoided in the real world, wherein it is reasonable to suggest that clinical judgment that weighs patient characteristics and indicated treatments is exercised in a prudent fashion. Furthermore, our data advocate the use of TMT as a first-line investigation modality in patients with suspected coronary syndromes, especially in those who are able to exercise. Although there have been concerns regarding the limited diagnostic power of TMT to rule in or rule out obstructive CAD,[21,22] we showed that TMT could be a cost-effective, easily assessable, and safe option for patients with suspected coronary syndromes who can exercise adequately and have an interpretable ECKG.[14,23,24] However, the lowest-risk patients were more likely to be included in the TMT group, and these patients may not derive benefit from any diagnostic change due to paucity of future events.[15] Further investigation of the clinical efficacy of deferred testing versus TMT or any other option for the lowest-risk patients with stable chest pain is still needed.

Our study had several limitations. First, the definitions of end point composites and comorbidities were determined on the basis of the diagnostic codes using claims data from the National Health Insurance Service database, which might have resulted in underestimation or overestimation. Second, clinical data such as patient symptoms and laboratory results were unavailable from the database. Third, these results reflect patterns of clinical practice and outcomes in South Korea. Fourth, tests conducted before the index test without meeting the inclusion criteria (eg, preoperative testing, general health checkups) and any additional downstream testing after the index test could potentially impact the study results. Despite these limitations, this study included longitudinal follow-up data from a national patient sample, and since the primary objective of the current study is to compare the clinical outcomes of initial gatekeeping studies in patients with suspected coronary syndromes, the influence of downstream tests might not undermine the main message of our study. Therefore, our findings reflect real-world use and outcomes of gatekeeping studies on a nationwide scale.

In conclusion, in this nationwide database cohort including patients with suspected coronary syndromes, the initial strategy of CCTA as a gatekeeper was not associated with better cardiovascular outcomes than functional testing. In clinical practice, gatekeeping studies should be conducted on the basis of patient characteristics.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3

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Supplemental Material

Table S1. ICD-10th codes used for the study endpoints.

Endpoints	**ICD-10 codes**
Cardiac death	"I20" "I21" "I22" "I60" "I61" "I62" "I63" "I64" "I25" "I11" "I13" "I42" "I46"
Myocardial infarction	"I21" "I22"
Revascularization	"M6551" "M6552" "M6553" "M6554" "M6561" "M6562" "M6563" "M6564" "M6565" "M6566" "M6567" "M6571" "M6572" "O1876" "O1877" "O1641" "O1642" "OA641" "OA642" "O1640" "O1647" "O1648" "O1649" "OA640" "OA647" "OA648" "OA649"

Table S2. Baseline characteristics of the patients according to the initial investigation modality after IPTW.

Characteristics	CCTA (n=26,571)	SPECT (n=24,967)	TMT (n=26,824)	P value
Age, years	54.4±14.3	54.7±13.4	54.1±14.3	0.33
Female sex, n (%)	12,602 (47.4%)	11,803 (47.3%)	12,645 (47.1%)	0.93
Comorbid conditions				
Hypertension, n (%)	13,673 (51.5%)	12,859 (51.5%)	13,816 (51.5%)	0.99
Hyperlipidemia, n (%)	14,628 (55.0%)	14,138 (56.6%)	14,783 (55.1%)	0.43
Diabetes mellitus, n (%)	10,477 (39.4%)	9,892 (39.6%)	10,628 (39.6%)	0.95
Heart failure, n (%)	1,681 (6.3%)	1,505 (6.0%)	1,675 (6.2%)	0.77
Chronic kidney disease, n (%)	592 (2.2%)	522 (2.1%)	624 (2.3%)	0.64
Atrial fibrillation, n (%)	1,123 (4.2%)	1,017 (4.1%)	1,165 (4.3%)	0.76
Hemorrhagic stroke, n (%)	355 (1.3%)	267 (1.1%)	353 (1.3%)	0.36
Ischemic stroke, n (%)	2,549 (9.6%)	2,223 (8.9%)	2,529 (9.4%)	0.46
Peripheral arterial occlusive disease, n (%)	2,147 (8.1%)	1,975 (7.9%)	2,172 (8.1%)	0.89
Previous aspirin use, n (%)	9,260 (34.9%)	8,720 (34.9%)	9,366 (34.9%)	0.99
Previous clopidogrel use, n (%)	1,509 (5.7%)	1,482 (5.9%)	1,559 (5.8%)	0.82
Previous statin use, n (%)	7,346 (27.6%)	7,180 (28.8%)	7,511 (28.0%)	0.54
Previous ACE inhibitor use, n (%)	2,966 (11.2%)	3,161 (12.7%)	2,976 (11.1%)	0.06
Previous ARB use, n (%)	6,928 (26.1%)	6,282 (25.2%)	6,835 (25.5%)	0.61
Previous beta blocker use, n (%)	7,881 (29.7%)	7,199 (28.8%)	8,000 (29.8%)	0.58
Charlson comorbidity index, mean	3.06±2.61	2.99±2.49	3.05±2.69	0.60

ACE = angiotensin-converting enzyme, ARB = angiotensin-receptor blocker, IPTW = inverse probability treatment weighting, CCTA = coronary computed tomography angiography, SPECT= single-photon emission computed tomography, TMT = treadmill test

Table S3. Initiation of medication within 90 days.

		Initiated	P value	Initiated (after IPTW)	P value (after IPTW)
Aspirin	**CCTA**	597 (7.6 %)	**CCTA vs. SPECT** P < 0.001 **CCTA vs. TMT** P < 0.001	1,981 (7.5 %)	**CCTA vs. SPECT** P < 0.001 **CCTA vs. TMT** P < 0.001
	SPECT	193 (10.4 %)		2,931 (11.7 %)	
	TMT	1,759 (10.2 %)		2,797 (10.4 %)	
Clopidogrel	**CCTA**	516 (6.6 %)	**CCTA vs. SPECT** P = 0.005 **CCTA vs. TMT** P = 0.63	1,641 (6.2 %)	**CCTA vs. SPECT** P = 0.003 **CCTA vs. TMT** P < 0.001
	SPECT	156 (8.4 %)		1,701 (6.8 %)	
	TMT	1,108 (6.4 %)		1,857 (6.9 %)	
Statin	**CCTA**	696 (8.9 %)	**CCTA vs. SPECT** P = 0.21 **CCTA vs. TMT** P = 0.03	2,299 (8.7 %)	**CCTA vs. SPECT** P < 0.001 **CCTA vs. TMT** P < 0.001
	SPECT	182 (9.8%)		2,397 (9.6%)	
	TMT	1,682 (9.7%)		2,729 (10.2%)	

CCTA = coronary computed tomography angiography, IPTW = inverse probability treatment weighting, SPECT = single-photon emission computed tomography, TMT = treadmill test