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Risk stratification of non-obstructive coronary artery disease for guidance of preventive medical therapy

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HIGHLIGHTS

- We developed a risk prediction model for patients with non-obstructive CAD by CCTA.
- The prediction model included clinical factors and extent of non-obstructive CAD.
- Statin therapy improved outcomes in the high-risk group by the prediction model.
- Use of aspirin was associated with worse outcomes in the low-risk group.
- The prediction model can guide preventive medical therapy for non-obstructive CAD.

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ABSTRACT

Background and aims: Given the potential benefit of medical therapy in patients with non-obstructive coronary artery disease (CAD), there is a need for risk stratification and treatment strategy for these patients. We aimed to develop a risk prediction model for non-obstructive CAD patients for risk stratification and guidance of statin and aspirin therapy.

Methods: From a cohort of consecutive patients who underwent coronary computed tomography angiography (CCTA) (n = 25,087), we identified patients with non-obstructive CAD of 1–49% diameter-stenosis (n = 6243) and developed a risk prediction model for 5-year occurrence of a composite of all-cause mortality, myocardial infarction, and late coronary revascularization using a derivation cohort (n = 4391).

Results: Age, sex, hypertension, diabetes, anemia, C-reactive protein, and the extent of non-obstructive CAD were incorporated in the prediction model (risk score 0-13, C-index = 0.716). Patients were categorized into 4 groups; risk score of 0–3 (low-risk), 4-6 (intermediate-risk), 7-9 (high-risk), and ≥10 (very high-risk). Patients with very high-risk demonstrated unfavorable outcome comparable to patients with obstructive CAD. The low-risk group exhibited favorable outcome similar to those with no CAD. While statin therapy was associated with better outcomes in high- or very high-risk group (hazard ratio, 0.62; 95% confidence interval, 0.39–0.96; $p = 0.033$), aspirin use was associated with an increased risk in low-risk group (hazard ratio, 2.57; 95% confidence interval, 1.34–4.90; $p = 0.004$).

Conclusions: A dedicated risk scoring system for non-obstructive CAD using clinical factors and CCTA findings

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accurately predicted prognosis. According to our risk prediction model, statin therapy can be beneficial for high-risk patients, whereas aspirin can be harmful for low-risk patients.

1. Introduction

Coronary computed tomography angiography (CCTA) has become increasingly used for risk stratification and decision-making regarding management in patients with suspected coronary artery disease (CAD). Compared with traditional approaches that focus on the evaluation of myocardial ischemia, CCTA directly visualize coronary atherosclerosis and allows for detection of non-obstructive CAD as well as obstructive CAD. Unlike invasive coronary angiography, which focuses on the presence of obstructive CAD, CCTA directly visualizes coronary atherosclerosis and allows for the detection of non-obstructive, as well as obstructive, CAD. Due to the lack of an obstructive lesion limiting coronary blood flow, non-obstructive CAD has often been regarded as "insignificant" or "non-significant" in the medical literature [1]. However, recent studies using CCTA have shown that the presence of non-obstructive CAD contributes to a higher risk of myocardial infarction (MI) and mortality [2,3].

Given several recent analyses that have demonstrated the benefit of preventive medications in patients with non-obstructive CAD [4–6], the presence of non-obstructive CAD itself provides valuable information to guide disease management. As non-obstructive CAD is relatively commonly observed (up to 50% of patients who underwent CCTA) [2,3,5], there is a need to provide enhanced risk stratification and individualized preventive management. Although there have been efforts to stratify the risk of cardiovascular events according to CCTA results [7,8], these studies were not focused on patients with non-obstructive CAD. Also, despite the well-established prognostic value of the extent of non-obstructive CAD [2,3], there have been little efforts to account for clinical risk factors along with the extent of CAD and to provide detailed risk stratification. In addition, whether the beneficial effects of preventive medications vary according to the stratified risk has not been well-evaluated. Therefore, we aimed to develop a risk prediction model incorporating clinical risk factors and the extent of coronary atherosclerosis in patients with non-obstructive CAD using a large retrospective cohort. In addition, we sought to determine the effect of statin and aspirin therapy in each risk group.

2. Patients and methods

2.1. Study population and source of data

The medical records of 29,564 consecutive adult patients < 80 years of age who underwent clinically indicated CCTA at two tertiary hospitals (Seoul National University Hospital and Seoul National University Bundang Hospital) between 2007 and 2011 were retrospectively reviewed. The patients underwent CCTA at the attending physician's discretion, based on the patient's symptoms or signs, or otherwise clinically suspected CAD. We obtained the resident registration numbers, demographic factors and laboratory test results of the study population. Total cohort was then linked to the Health Insurance Review and Assessment Service (HIRA) claims data, which includes all information regarding medical services provided to each individual of the entire Korean population, including date, site, medications, diagnosis, procedures, hospitalization and survival [6,9]. Comorbidities were identified in the HIRA database using diagnostic codes, and prescription information. Patients were excluded if they had prior MI (n = 1840), prior coronary revascularization (n = 419), or malignancy (n = 2216). Patients with uninterpretable CCTA images (n = 2) were also excluded. CCTA results of the remaining 25,087 symptomatic patients were reviewed: 16,635 patients did not have any CAD by CCTA

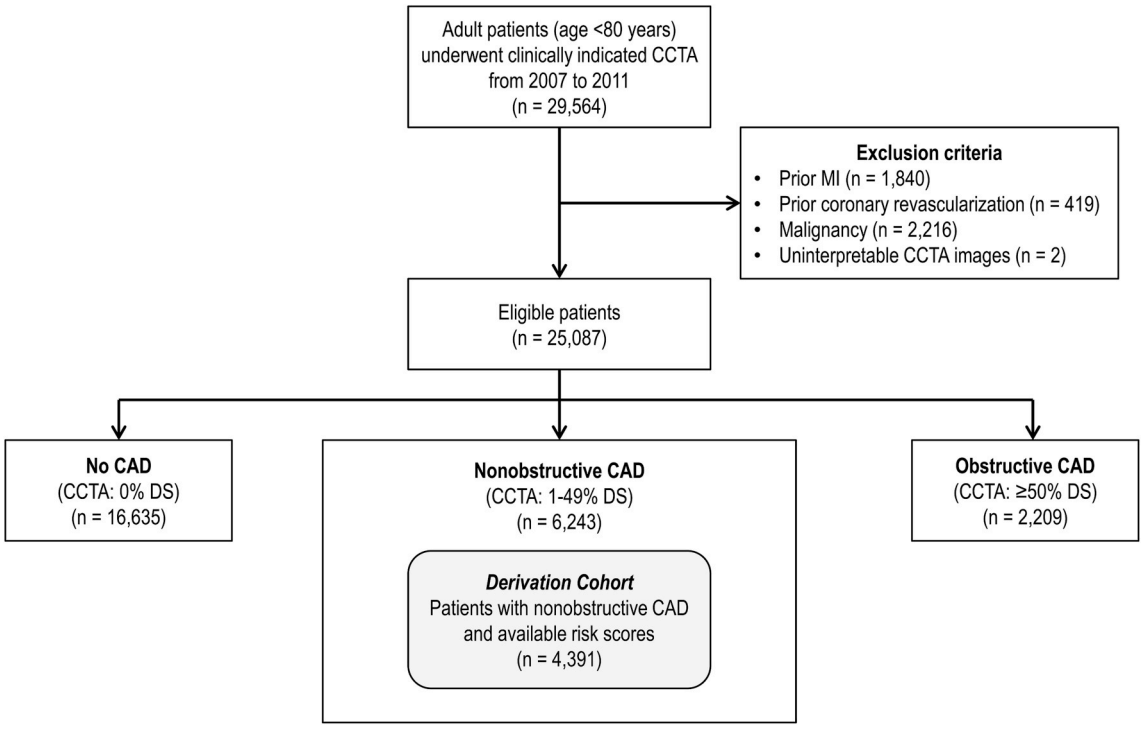

Fig. 1. Study population.
Patients with non-obstructive CAD (n = 6,243) were identified from a cohort of patients who underwent clinically indicated CCTA. Risk prediction model was developed using the *derivation cohort* (n = 4, 391).

(0% diameter-stenosis [DS]), 6243 patients had non-obstructive CAD (1–49% DS), and 2209 patients had obstructive CAD (≥50% DS) (Fig. 1, Supplementary Table 1). This study was carried out according to the principles of the Declaration of Helsinki and was approved by the institutional review board of each participating institution.

2.2. CCTA image acquisition and analysis

Unenhanced computed tomography (CT) and contrast-enhanced coronary CT angiograms were performed using a 64-detector row CT scanner (SOMATOM Sensation 64 and SOMATOM Definition, Siemens Medical Solutions, Forchheim, Germany; Brilliance 64, Philips Medical Systems, Best, The Netherlands) according to the established guidelines [10]. CCTA images were independently analyzed by a cardiac radiologist who was blinded to the clinical information. Coronary artery calcium scores (CACS) were measured using the Agatston scoring system. A coronary atherosclerotic plaque was defined as any clearly discernible lesion with an area > 1 mm^2 that could be discriminated from the coronary artery in at least 2 independent image planes [11]. According to the maximal DS, patients were categorized as having no CAD (0% DS), non-obstructive CAD (1–49% DS), or obstructive CAD (≥50% DS). In patients with non-obstructive CAD, the number of epicardial arteries with coronary atherosclerotic plaques was counted (from 1 to 3) and used as the vessel score to reflect the extent of non-obstructive CAD.

2.3. Outcome measures

Study outcome was a composite of all-cause mortality, MI, and late coronary revascularization (> 90 days after CCTA) [6,11]. Databases from HIRA and the Korean Ministry of Security and Public Administration were cross-checked to confirm deaths and the date of death [6,9]. The occurrence of MI and coronary revascularization was identified using diagnostic and reimbursement codes from the HIRA claims data. Early coronary revascularization (within 90 days after CCTA) was censored at the time of the procedure to exclude any CCTA-driven revascularization from clinical events [6].

2.4. Statistical analysis

2.4.1. Development of a risk prediction model for non-obstructive CAD

The variables assessed for the risk prediction model were age, sex, hypertension, diabetes mellitus (DM), hypercholesterolemia, atrial fibrillation (AF), heart failure (HF), chronic kidney disease (CKD), chronic obstructive pulmonary disease, stroke, body-mass index, hemoglobin, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting glucose, hemoglobin A1c (HbA1c), blood urea nitrogen (BUN), creatinine, high-sensitivity C-reactive protein (hsCRP), CACS, and vessel score. The risk prediction model was developed using the "*derivation cohort*", which consisted of 4391 non-obstructive CAD patients with complete data for the candidate variables (Fig. 1). Differences in baseline characteristics and study outcomes between the non-obstructive CAD patients (n = 6243) and the *derivation cohort* (n = 4391) were evaluated using standardized difference analysis (Supplementary Table 2).

In order to develop a relevant and practical risk prediction model, patient age was categorized as < 60 years, 60–69 years, and ≥70 years. The extent of non-obstructive CAD was categorized in two groups by CCTA (3-vessel involvement vs. 1- or 2-vessel involvement), because this provided a better risk stratification in our study population (Supplementary Table 3) [3,12]. The CACS was categorized as < 100 and ≥ 100, considering the clinical guidelines and the applicability in real-world practice [13–15]. CACS > 100 is associated with a greater reduction in the risk for major adverse cardiovascular events with statin therapy compared to that with CACS < 100, based on the results of a previous large cohort study [16]. These findings support the current role of CACS as an indicator of the coronary atherosclerotic plaque burden of the individual patient rather than individual plaque vulnerability [14]. Although we also considered categorizing CACS into 3 groups by adding a group of CACS ≥400, the number of patients with non-obstructive CAD and CACS ≥400 was too small (3.8% of the study population) (Supplementary Fig. 1), and this approach did not provide a better risk stratification (Supplementary Fig. 2). As the use of CACS in symptomatic patients has been limited by the high background prevalence of CAC and its low specificity for obstructive CAD [17], we developed a risk prediction model that included the extent of non-obstructive CAD by CCTA without CACS (*model 1*). We also developed a risk prediction model using both the extent of non-obstructive CAD and CACS (*model 2*).

For the *derivation cohort* (n = 4132), univariable logistic regression analyses were performed to examine the effect of the candidate predictors on the 5-year study outcomes. Multivariable analyses were performed to select the independent predictors that would be included in the prediction models. Among the candidate variables, body-mass index, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum creatinine, fasting glucose, and HbA1c were excluded due to their multicollinearity (variance inflation factor > 4). The logistic coefficients (β), which were obtained from the multivariable logistic regression analysis, were utilized to assign the risk score. The lowest coefficient among the selected predictive variables (β_{lowest}) was set as a risk score of 1, and the integer values rounded to the nearest multiple of the coefficients of the other predictive variables (β_i), divided by the lowest coefficient (min [β_1, β_2, …, β_k]) were assigned as the risk scores for each variable.

$$Risk\ Score_i = \left[\frac{\beta_i}{\min(\beta_1, \beta_2, \cdots, \beta_k)} \right]$$

Both internal and external validation analyses were performed for the developed risk prediction models. Internal validation was performed using the 10-fold cross-validation method [18], dividing the *derivation cohort* at random into 10 approximately equally sized parts. External validation was performed using the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging (PARADIGM) registry, which is a multi-national prospective observational registry to characterize the natural history of CAD in relation to clinical and laboratory data [19], and another retrospective cohort of suspected CAD patients who underwent CCTA from the Boramae Medical Center in Seoul, South Korea [20].

2.4.2. Subgroup analysis

The *derivation cohort* was categorized into 4 groups according to risk score using the K-means clustering method; low, intermediate, high, and very high risk group. Clinical outcomes were compared between these risk groups, as well as with those with no CAD, and those with obstructive CAD, using Kaplan-Meier method with log-rank test. Clinical usefulness of statin and aspirin therapy initiated upon detection of non-obstructive CAD was assessed across the risk groups, using Kaplan-Meier method with log-rank test and Cox proportional hazard regression analysis. For the between-group comparisons, patients with high risk and very high risk were combined due to the small number of patients in these groups. Considering the usual clinical practice of the participating institutions as well as previous reports [21,22], we defined the patients who were on a statin or aspirin at day 60 after the index CCTA as "statin users" or "aspirin users", respectively.

All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA) and R 3.3.0 (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Study population and baseline characteristics

The baseline characteristics of patients with non-obstructive CAD (n = 6243) were compared to those of patients without CAD (n = 16,635) and those of patients with obstructive CAD (n = 2209) (Supplementary Table 1). The mean age and the prevalence of conventional cardiovascular risk factors were proportional to the severity of CAD. The baseline characteristics including clinical variables and CCTA results of patients in the *derivation cohort* (n = 4391) (Table 1) were also compared to the entire non-obstructive CAD cohort (n = 6243), showing no significant differences between the two cohorts (Supplementary Table 2).

3.2. Development of the risk prediction model

Until 5 years of follow-up, the composite endpoint occurred in 262 of 4391 patients with non-obstructive CAD (6.0%, annualized event rate 1.3%): 100 patients died (2.3%), 77 patients had MI (1.8%), and 125 patients underwent late coronary revascularization (2.8%) (Supplementary Table 4). Univariable logistic regression analysis showed that advanced age, hypertension, DM, hypercholesterolemia, AF, HF, chronic obstructive pulmonary disease, stroke, anemia, BUN ≥20 mg/dL, hsCRP ≥1.0 mg/L, 3-vessel involvement of non-obstructive CAD, and a CACS ≥100 were significantly associated with the 5-year risk of the composite endpoint (Supplementary Table 5). When we performed multivariable analysis without CACS (*model 1*), advanced age, male sex, hypertension, DM, anemia, hsCRP ≥1.0 mg/L, and 3-vessel involvement of non-obstructive CAD remained independent predictors for the cardiovascular events. Similar results were observed in the multivariable analysis with the CACS (*model 2*), demonstrating that CACS ≥100 is also an independent predictor (Supplementary Table 5).

Finally, advanced age, male sex, hypertension, DM, anemia, hsCRP ≥1.0 mg/L, 3-vessel involvement of non-obstructive CAD, and a CACS ≥100 were included in the final risk prediction model (Table 2). Using the regression coefficient (β) obtained from the multivariable analysis, we determined the relative contribution of each factor to the prediction of cardiovascular events. The assigned risk scores were 1 point for age 60–69 years and 3 points for age ≥70 years, 1 point for male sex, 2 points for hypertension, 1 point for DM, 3 points for anemia, 1 point for hsCRP ≥1.0 mg/L, 2 points for 3-vessel involvement in *model 1* and 1 point in *model 2*, and 2 points for a CACS ≥100 in *model 2*. The total score was 13 for *model 1* and was 14 for *model 2*. The C-indices of prediction *model 1* and *model 2* were 0.716 and 0.721, respectively (Supplementary Fig. 3). The internal validation revealed an accuracy of 0.938 for both *model 1* and *model 2*. When we performed external validation using the PARADIGM multinational prospective registry [19], the risk scores according to the risk prediction *model 1* were available in 238 patients with non-obstructive CAD from the PARADIGM registry, and the C-index was 0.751. *Model 2* was not applicable to the PARADIGM registry due to the lack of CACS data. We performed additional external validation using another separate CCTA cohort from Boramae Medical Center in South Korea: among 169 patients with non-obstructive CAD in the cohort, the C-indices were 0.780 and 0.752 for *model 1* and *model 2*, respectively [20].

3.3. Risk scores and the occurrence of cardiovascular events

According to the risk prediction *model 1*, the *derivation cohort* was categorized into the following groups: a low-risk group (risk scores, 0 to 3; n = 1821), intermediate-risk group (4–6; n = 2049), high-risk group (7–9; n = 357), and very high-risk group (≥10; n = 164) (Supplementary Fig. 4). Kaplan-Meier survival curves displayed a stepwise increase in the risk for the composite endpoint with increasing risk scores (Fig. 2). Notably, the low-risk group showed a favorable outcome comparable to that of subjects with no CAD (5-year event-free survival rate, 97.5% vs 96.9%; log-rank $p = 0.164$), and the very high-risk group demonstrated an unfavorable outcome similar to those with obstructive CAD (5-year event-free survival rates, 75.9% vs. 79.2%; log-rank $p = 0.413$). Similar results were observed when the patients were categorized according to the risk prediction *model 2*.

3.4. Risk prediction model for guidance of medical therapy

In the *derivation cohort* (n = 4391), 1522 patients (34.7%) were statin users and 1397 patients (31.8%) were aspirin users. The adherence rates to statin and aspirin until 1 year and 5 years of follow-up were assessed in each risk group (Supplementary Table 6). The medication possession ratio (MPR) for statin ranged from 84.4% to 98.4% until 1 year of follow-up, and from 66.7% to 95.3% until 5 years of follow-up. The MPR for aspirin ranged from 88.1% to 97.3% and from 60.5% to 83.8% until 1 year and 5 years of follow-up, respectively.

The use of statin was associated with a significantly low risk of cardiovascular events among the high- and very high-risk groups (risk score, ≥7; n = 521) (log-rank $p = 0.030$; HR, 0.62; 95% CI, 0.39–0.96; $p = 0.033$) (Fig. 3A). However, statin use was not associated with reduced cardiovascular events in the low-risk group (risk score, 0 to 3; n = 1821) and intermediate-risk group (risk score, 4 to 8; n = 2049) (Fig. 3B and C). Of note, while aspirin therapy was not associated with study outcomes in the intermediate- and high-risk groups, the use of aspirin was significantly associated with increased cardiovascular events in the low-risk group (log-rank $p = 0.008$; HR, 2.57; 95% CI, 1.34–4.90; $p = 0.004$) (Fig. 3D–F).

In order to provide more detailed information on the outcomes, the association between medical therapy use and the risk of all-cause mortality was assessed in the subgroups according to risk scores (Supplementary Fig. 5). In the high- and very high-risk groups, statin users had a significantly lower risk of mortality compared to that in the non-users (log-rank $p = 0.002$; HR, 0.37; 95% CI, 0.20–0.71; $p = 0.003$). An association between statin use and lower mortality risk

Table 1
Baseline characteristics of patients with non-obstructive CAD.

	Patients with non-obstructive CAD and available risk scores (*derivation cohort*) (n = 4391)
Age (years)	60.0 ± 9.8
Male sex	2961 (67.4%)
Body-mass index (kg/m^2)	24.8 ± 2.7
Systolic blood pressure (mmHg)	128.2 ± 14.6
Diastolic blood pressure (mmHg)	78.7 ± 9.4
Comorbidities	
Hypertension	1900 (43.3%)
DM	740 (16.9%)
Hypercholesterolemia	1135 (25.8%)
AF	175 (4.0%)
HF	155 (3.5%)
CKD	373 (8.5%)
Stroke	431 (9.8%)
Laboratory findings	
Hemoglobin (g/dL)	14.6 ± 1.6
Total cholesterol (mg/dL)	198.3 ± 42.7
BUN (mg/dL)	15.0 ± 5.5
Creatinine (mg/dL)	1.0 ± 0.4
hsCRP (mg/L)	4.3 ± 19.9
CACS	75 ± 180.2
CACS < 100	3525 (80.3%)
CACS ≥100	866 (19.7%)
Vessel score (extent of non-obstructive CAD)	
1VD	2511 (57.2%)
2VD	1280 (29.2%)
3VD	600 (13.7%)

Data are shown as number (%) or mean ± standard deviation.

Table 2
Development of the risk prediction model.

	Model 1[a]					Model 2[b]				
	Adjusted OR	95% CI	*p* value	B	Risk score	Adjusted OR	95% CI	*p* value	β	Risk score
Age (years)										
≥60 years (*versus* < 60 years)	1.44	1.03–2.01	0.0310	0.3655	1	1.39	0.99–1.94	0.0552	0.3266	1
≥70 years (*versus* < 60 years)	2.48	1.75–3.50	< 0.0001	0.9062	3	2.30	1.62–3.28	< 0.0001	0.8347	3
Male sex	1.38	1.03–1.84	0.0314	0.3190	1	1.34	1.00–1.80	0.0471	0.2952	1
Hypertension	1.69	1.27–2.25	0.0003	0.5242	2	1.62	1.21–2.16	0.0010	0.4819	2
DM	1.43	1.05–1.93	0.0225	0.3541	1	1.42	1.04–1.92	0.0256	0.3469	1
Anemia[c]	2.46	1.69–3.57	< 0.0001	0.8992	3	2.41	1.66–3.50	< 0.0001	0.8779	3
High hsCRP (≥1.0 mg/L)	1.46	1.12–1.90	0.0046	0.3804	1	1.47	1.13–1.91	0.0044	0.3834	1
3VD (*versus* 1VD or 2VD)	1.79	1.32–2.44	0.0002	0.5830	2	1.43	1.01–2.03	0.0424	0.3600	1
CACS ≥100 (*versus* < 100)	*Not applicable*					1.58	1.15–2.17	0.0052	0.4560	2
Total risk score					13					14

[a] *Model 1* incorporates the clinical risk factors and the extent of non-obstructive CAD.
[b] *Model 2* incorporates the clinical risk factors, extent of non-obstructive CAD, and CACS.
[c] Anemia was defined as a hemoglobin level of < 13 g/dL for men and < 12 g/dL for women.

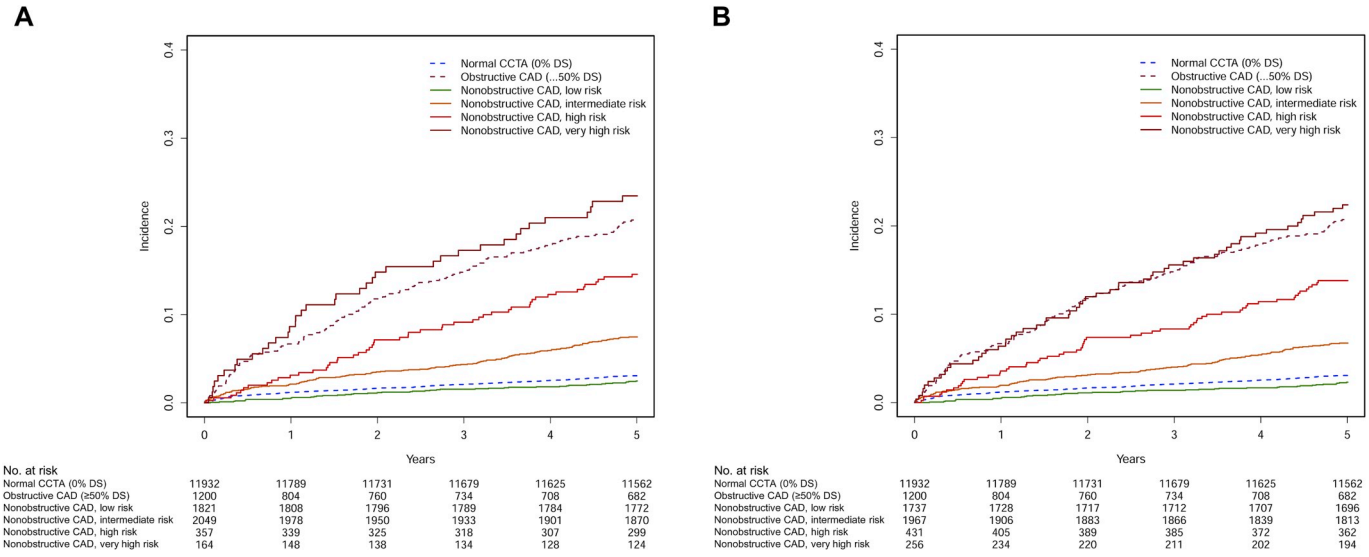

Fig. 2. Risk stratification of the patients with non-obstructive CAD.
The 5-year occurrences of a composite of all-cause mortality, MI, and late coronary revascularization are shown according to the risk scores derived from the risk prediction models: (A) *model 1* used clinical characteristics and the vessel score, and (B) *model 2* used clinical characteristics, the vessel score, and CACS.

was not observed in the low-risk and intermediate-risk groups. The use of aspirin was not associated with the risk of all-cause mortality, regardless of the risk group.

4. Discussion

In the present study, we developed a risk prediction model exclusively in patients with non-obstructive CAD detected by CCTA. The prediction model revealed that the cardiovascular risk of patients with non-obstructive CAD can be stratified from a low level comparable to those with no CAD, to a high level similar to those with obstructive CAD. Statin therapy was associated with better outcomes in the high-risk group, but not in the low- and intermediate-risk groups. Use of aspirin was associated with worse outcomes in the low-risk group and did not affect the outcome of other risk groups. Our findings suggest that the cardiovascular risk of non-obstructive CAD can be further stratified using clinical factors and CCTA findings, and that risk stratification can be utilized for the guidance of preventive medical therapy.

Cardiovascular risk of non-obstructive CAD has become apparent as a result of large-scale CCTA registries [3,5]. Although the overall risk of cardiovascular events due to non-obstructive CAD is not as high as that due to obstructive CAD, its socioeconomic burden cannot be overlooked, considering its higher prevalence [2,3,5]. Given the potential benefit of preventive medical therapy that has been consistently reported in recent studies, there is a clinical need for a risk stratification and treatment strategy for these patients [4–6]. However, there has been little effort to stratify the risk for patients with non-obstructive CAD and to prioritize active treatment for those who can benefit from it. Although several large-scale registries have proposed risk score calculators using CCTA results [7,8], these prediction models mainly focused on patients with obstructive CAD or high CACS. In that reason, we developed risk scoring system dedicated to non-obstructive CAD in the present study.

The risk of cardiovascular events is proportional to the extent of non-obstructive CAD [2,3]. In a prospective study of 2583 consecutive patients with < 50% DS by CCTA, *Lin* et al. demonstrated a graded relationship between the number of affected vessels and the mortality risk: patients with 3-vessel involvement of non-obstructive CAD had a significantly higher risk of mortality compared to those with no CAD, whereas those with 1-vessel involvement were not [3]. The prognostic value of the extent of non-obstructive CAD was further demonstrated in a cohort study of more than 3000 patients who underwent CCTA [2].

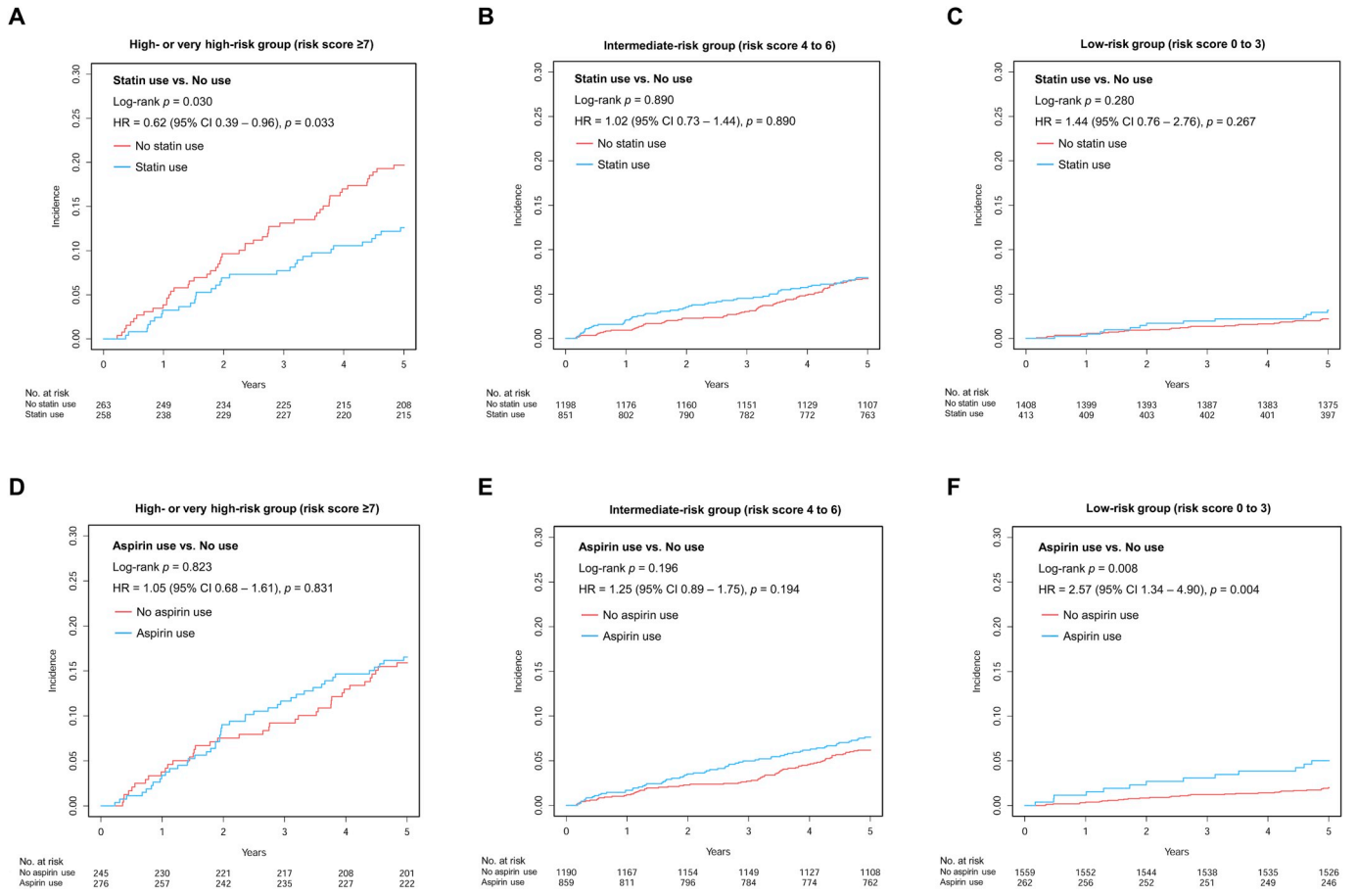

Fig. 3. Associations between the use of statin and aspirin with the 5-year occurrence of the composite endpoint.
(A-C) Statin use was associated with a lower risk of cardiovascular events in the high- or very high-risk group (risk score ≥7), but not in the low- and intermediate-risk groups. (D–F) Use of aspirin was not associated with a lower risk of cardiovascular events in the high-and intermediate-risk group, but was associated with a higher risk of cardiovascular events in the low-risk group.

Compared to those with no CAD by CCTA, patients with nonextensive non-obstructive CAD (segment involvement score ≤4) did not have a higher risk of cardiovascular events. However, the risk of cardiovascular events due to extensive non-obstructive CAD (segment involvement score > 4) was significantly higher than that in patients without CAD, and was even comparable to the risk due to obstructive CAD. Our prediction model is also based on the prognostic significance of the extent of non-obstructive CAD: after adjusting for clinical risk factors, the patients with 3-vessel involvement were at a 1.8-fold higher risk of cardiovascular events than those with 1- or 2-vessel involvement, and the patients with a CACS ≥100 had a 1.6-fold higher risk of events than those with a CACS < 100.

In addition to coronary atherosclerosis and conventional risk factors, we also included anemia and elevated hsCRP in the final prediction model. Consistent with previous studies [23], we found an independent association between elevated hsCRP and adverse cardiac events, suggesting that chronic inflammation serves as an important risk factor in patients with non-obstructive CAD. However, statistical independence does not establish the use of hsCRP as an adjunct in global risk assessment. Although our risk stratification algorithm with hsCRP could identify the high-risk patients who might benefit from statin treatment, further studies are still required to assess the viability of hsCRP for risk stratification and preventive medical treatment guidance. Additionally, anemia was an independent risk factor in patients with non-obstructive CAD and was included in our risk prediction model. Anemia may predispose individuals to myocardial ischemia and vulnerable coronary plaques [24], and may result in symptom-driven coronary revascularization and the occurrence of acute coronary syndrome [25–27]. However, current evidence linking therapeutic changes in anemia to the prevention of adverse cardiovascular events is insufficient and further studies are required.

From a practical viewpoint, it is important to assess whether risk stratification of patients with non-obstructive CAD could result in different treatment strategies. Although it is largely accepted that patients with non-obstructive CAD need medical therapy, current clinical guidelines do not provide specific recommendations regarding the appropriate treatment for these patients, leaving room for improvement [7,28]. Several studies suggested that statin is beneficial in patients with non-obstructive CAD. A study of the CONFIRM registry found a 68% lower risk of mortality with statin therapy in patients with non-obstructive CAD [5]. Our group also previously demonstrated similar results: statin therapy initiated after CCTA was associated with a 60% reduction in the risk of mortality and coronary revascularization [6]. However, these studies did not take account of individual risk and the extent of non-obstructive CAD. On the other hands, *Hulten* et al. suggested the potential benefit of statin therapy according to the extent of non-obstructive CAD. In the study of 2839 patients who underwent CCTA, the authors revealed that statin use after CCTA was associated with reduced cardiovascular death and MI in patients with extensive non-obstructive CAD (> 4 segments involvement) but not in those with ≤4 segments involvement [4]. However, the study did not try to incorporate clinical risk factors such as diabetes. Adding to these previous studies, we provided a risk scoring system incorporating the extent of non-obstructive CAD along with clinical risk factors. And we found the potential benefit of statin therapy for those with high risk scores indicating the presence of extensive non-obstructive CAD and/or multiple

risk factors. Although the impact of statin therapy was retrospectively assessed, the present study sets the stage for prospective trials, which are required to evaluate whether the further risk stratification of non-obstructive CAD can be utilized for statin therapy guidance. The impact of statin intensity also needs to be further evaluated.

In addition, our results suggest that aspirin use should not be recommended to patients with non-obstructive CAD if the patients have low risk scores. A previous report suggested that aspirin had no beneficial effects in patients with non-obstructive CAD [5]. However, our study is the first to investigate the effect of aspirin in patients with non-obstructive CAD stratified according to risk score, and to demonstrate the potential harm of aspirin in low-risk patients. Our findings can be interpreted alongside recent trials that reported the lack of benefits of aspirin as a primary prevention, because reduced ischemic events due to aspirin are neutralized by the increased bleeding risk [29,30]. According to the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial of 12,546 patients with an average cardiovascular risk, the use of aspirin did not reduce the occurrence of cardiovascular death, acute coronary syndrome, stroke, or transient ischemic attack, but did increase bleeding risk [29]. Even in patients with DM, A Study of Cardiovascular Events in Diabetes (ASCEND) demonstrated that the reduced risk of a vascular event was counterbalanced by the increased bleeding risk [30]. These trials suggest that individual risks should be assessed when considering aspirin as a preventive measure. Likewise, the assessment of risk profiles is important in patients with non-obstructive CAD, as the use of aspirin was harmful for low risk patients.

Given that statin and aspirin prescriptions significantly increase upon abnormal findings by CCTA [4,21], tailored treatment for non-obstructive CAD would improve the prognosis of these patients and contribute to the socio-economic impact. Our risk stratification algorithm may allow for the tailored use of preventive medication according to the individualized risk (Supplementary Fig. 6). However, the lack of an association between statin therapy and outcomes in the lower risk patients with non-obstructive CAD in our study does not exclude the possible benefit of statin in these patients. Additionally, the potential harmful effect of aspirin in low-risk patients should be assessed in terms of the risk of major bleeding and the use of other medications, such as proton pump inhibitors or anticoagulants. Certainly, large-scale randomized trials are required before the risk score can be used to facilitate personalized decision-making regarding aspirin or statin therapy.

4.1. Limitations

Our study is subject to a number of limitations. First, our study should be interpreted in the context of inherent limitations related to its retrospective design. However, we identified the study population in a consecutive manner, and internal and external validation of our prediction models demonstrated appropriate predictive power. Second, detailed information on the other established risk factors, such as smoking status and family history, were not available in our retrospective cohort. Additionally, because we could not precisely differentiate cardiovascular death in the retrospective cohort, we included all-cause mortality in the composite endpoint. Instead, to minimize the potential influence of non-cardiovascular death, we excluded patients who were elderly (age $\geq$80 years) and those who had malignancy from the analysis. Furthermore, because our cohort was linked to the national claims data, which contains all information regarding medical services for the entire population, we were able to obtain accurate data on other study outcomes such as MI and coronary revascularization. Finally, our simplified risk scoring system used categorical variables rather than continuous variables. In addition, we assessed the extent of non-obstructive CAD based on a per-vessel analysis, rather than on a per-segment analysis. Although this could have negatively affected the statistical power, the overall prediction was appropriate. Most importantly, we aimed to develop a clinically feasible and easily applicable risk scoring system.

4.2. Conclusion

We developed a risk scoring system dedicated to non-obstructive CAD patients that provided effective risk stratification. According to our risk scoring system, statin therapy was associated with better clinical outcomes in the high-risk group, and aspirin therapy was associated with worse outcomes in the low-risk group. Our findings suggest that the cardiovascular risk of non-obstructive CAD can be further stratified using clinical factors and atherosclerosis burden, and that risk stratification can be utilized for guidance of medical treatment.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

Research idea and study design: ICH, HL, YEY; data acquisition: ICH, HL, YEY, ISC, HLK, HJC, JYL, JAC, HJK, GYC, JBP, SPL, HKK, YJK, DWS; data analysis and interpretation: ICH, HL, YEY, ISC, JYL; statistical analysis: ICH, ISC, JYL, JAC, HJK; supervision and mentorship: YEY, ISC, GYC, YJK. Each author contributed important intellectual content in writing the manuscript and accepts accountability for the overall work by confirming that questions pertaining to the accuracy or integrity of any portion of the work have been appropriately investigated and resolved. YEY and ISC confirm that this study has been reported honestly, accurately, and transparently, that no important aspects of the study have been omitted, and that any discrepancies from the planned study have been explained.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.09.018.

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