Outcomes and Associated Factors of Discrepant Coronary and Carotid Atherosclerosis

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Summary

Some patients exhibit discrepancies in carotid and coronary artery atherosclerosis. This study aimed to define the characteristics and prognosis of these discrepant patients and determine the best strategy to detect pan-vascular atherosclerosis. A database of 5,022 consecutively registered patients who underwent both coronary angiography and carotid ultrasonography, along with clinical and blood laboratory tests, echocardiography, and pulse wave velocity (PWV), was analyzed. The development of cerebro-cardiovascular (CV) events during the follow-up period was also evaluated. A significant proportion of patients (n = 1,741, 35%) presented with a discrepancy between carotid artery plaque and coronary artery disease (CAD). In patients without carotid plaque, male sex (odds ratio [OR], 1.71; 95% confidence interval [CI], 1.20-2.41; P = 0.003), older age (OR, 1.03; 95% CI, 1.01-1.04; P = 0.002), smoking history (OR, 1.58; 95% CI, 1.13-2.20; P = 0.008), lower high-density lipoprotein (HDL)-cholesterol level (OR, 0.97; 95% CI, 0.96-0.98; P < 0.001), and lower common carotid artery end-diastolic velocity (CCA-EDV) (OR, 0.97; 95% CI, 0.95-0.99; P = 0.005) were independently related to the presence of CAD. In patients without CAD, increased PWV was independently related to the presence of carotid plaque. In survival analysis, patients with isolated CAD had a higher probability of composite CV events; those with isolated carotid plaque had a higher probability of heart failure (HF) and mortality than their counterpart groups (P < 0.05). Even in patients without carotid artery plaque, careful coronary evaluation is needed in older or male patients with smoking history, lower HDL-cholesterol level, or lower CCA-EDV. Carotid plaque may be a potential risk factor for HF.

Key words: Coronary artery disease, Cardiovascular events, Arterial stiffness, Heart failure

Atherosclerosis is known to be a result of systemic diseases such as dyslipidemia, hypertension, and diabetes, the so-called coronary risk factors, and local hemodynamic characteristics may contribute to these systemic risk factors. Coronary artery disease (CAD), cerebrovascular disease, and peripheral artery disease are members of pan-vascular disease and share common atherosclerotic risk factors and pathogenesis. Increased carotid intima-media thickness (IMT) and the presence of plaque are widely utilized as screening markers of pan-vascular atherosclerosis, especially CAD. However, some patients show a discrepancy between carotid and coronary artery atherosclerosis, and it has been reported that the extent of carotid atherosclerosis is weakly correlated with the extent of coronary artery atherosclerosis and acute coronary syndrome, which may suggest that a differential mechanism may exist between carotid atherosclerosis and coronary atherosclerosis. Interestingly, these patients show slight differences in plaque morphology, tissue characteristics, blood flow patterns, and collaterals. However, current management guidelines are not specific to individualized atherosclerosis sites and are based on generalized risk scores, such as Framingham risk score (FRS). Thus, this study aims to define the characteristics and prognosis of these discrepant patients and determine the best strategy for detecting pan-vascular atherosclerosis.

Methods

Study population and endpoints: This study is a retrospective, observational, single-center study. The study protocol was approved by our institutional review board (3-2014-0215), and the need for informed consent was waived because of the retrospective study design. Overall,
5,022 patients who underwent consecutive carotid ultrasonography from March 2007 to March 2012 and coronary angiography within 1 year were analyzed.

Composite endpoints were defined as all cardiovascular (CV) events, consisting of myocardial infarction, unstable angina, and death from CV events. All-cause mortality, admission for heart failure (HF) aggravation, and new-onset cerebrovascular accident (CVA) were also used as follow-up endpoints. A coordinator reviewed the medical records to evaluate clinical outcomes.

Collection of clinical and blood laboratory findings: To determine the smoking status and the presence of hypertension, diabetes, dyslipidemia, atrial fibrillation, previous CVA, myocardial infarction, and HF, the medical history of patients was reviewed. Laboratory data, including estimated glomerular filtration rate (eGFR), total cholesterol level, high-density lipoprotein (HDL)-cholesterol level, and low-density lipoprotein (LDL)-cholesterol level, measured within 6 months, were also collected. For the general CV risk assessment (CAD, CVA, peripheral artery disease, and HF), modified FRS was calculated.6) The medication records were collected at the time of carotid ultrasonography.

Carotid ultrasonography, Doppler, and echocardiography: Carotid ultrasound was performed for pan-vascular screening in patients with coronary risk factors and for peripheral arterial evaluation after coronary interventions or ischemic stroke. The presence of carotid plaque was analyzed using carotid ultrasonography with/without Doppler. Ultrasonograms were acquired in end-diastole (defined as the R wave of an electrocardiogram) using the Registry of Diagnostic Cardiac Sonographers, which is equipped with an 11-MHz imaging transducer (Vivid-7 or Vivid E9, General Electric Ultrasound, Milwaukee, WI, USA; SC2000, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA; or Sonos 7500 or iE33; Philips Medical Systems, Andover, MA, USA). With the patient in the supine position and with slight hyperextension of the neck, the common carotid artery (CCA), carotid bulb, extracranial internal carotid artery (ICA), external carotid artery (ECA), and vertebral arteries were identified. All carotid measurements were performed with each vendor using semiautomated vessel-wall detection software. Following short-axis two-dimensional image acquisition of the CCA, long-axis B-mode ultrasonograms were acquired for subsequent measurements. Carotid measurements included IMT of the far vessel wall at a site approximately 1 cm away, proximal to the carotid bulb. The averaged IMT values of the left and right CCAs were subsequently used in all analyses. Plaque was defined as a protrusion of the vessel wall into the arterial lumen of at least 0.5 mm, with an IMT 50% of that of the surrounding sites or IMT of > 1.5 mm. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) of the CCA, ECA, and ICA were measured using a semiautomatic analysis system. Additionally, plaques were classified according to the number of carotid plaques: none, one (only on one side), and two (on both sides). In the carotid Doppler evaluation, we measured the PSV and EDV in both CCA, ICA, ECA, and vertebral arteries.3) In patients with atrial fibrillation, the average value of five consecutive beats was used for the analysis. Echocardiographic results (n = 4,752) of left ventricular (LV) ejection fraction (LVEF), left atrial volume index (LAVI), LV mass index (LVMi), and the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e') (E/e' ratio) were collected. The LV end-systolic wall stress index was calculated as described in a previous study.8)

Measurement of pulse wave velocity and the ankle-brachial index by tonometry: The values of brachial-ankle pulse wave velocity (baPWV) were simultaneously measured (n = 3,543) using a vascular testing device for applation tonometry (VP-2000; Colin Medical Technology, Komaki, Japan). After patients had rested in the supine position for > 5 minutes, bilateral brachial and posterior tibial artery pressure waveforms were stored for 10 seconds by an extremity cuff connected to an oscillometric pressure sensor. The distance between the two sampling points was calculated based on the height of the patient, and the transit time was automatically determined from the time delay between the proximal and distal waveforms. The baPWV was calculated as the distance between the two arterial recording sites divided by the transit time.9,10) To evaluate the peripheral atherosclerosis, the ankle-brachial blood pressure index (ABI) was analyzed (n = 3,551).

Coronary angiography: All patients who underwent coronary angiography met indications for invasive coronary angiography, such as stable angina pectoris, acute coronary syndrome, silent myocardial ischemia, suspected CAD in coronary CT, positive exercise ECG, and regional wall motion abnormality in echocardiography or pre-cardiac surgery evaluation. Coronary angiograms were analyzed by qualified interventional cardiologists, and visual estimation or qualitative analysis with the CAAS system (Pie Medical Imaging, Maastricht, The Netherlands) was used to assess the degree of luminal narrowing.11)

Definitions: Carotid plaque was defined as the presence of carotid plaque on at least one side of the CCA, ECA, or ICA. CAD was defined as ≥ 50% luminal narrowing at least one coronary artery on coronary angiography or previous history of revascularization. Patients were divided into four groups according to the presence of CAD and CA plaque: group I had neither CAD nor carotid plaque; group II had CAD, but no carotid plaque; group III had carotid plaque, but no CAD; and group IV had both CAD and carotid plaque (Figure 1).

Statistical analyses: Differences in clinical characteristics, risk factors, carotid ultrasound parameters, and peripheral tonometry indexes were tested using analysis of variance (continuous variables) with post hoc analysis and Dunnett correction or the chi-square test (categorical variables). The Kruskal-Wallis test was used to analyze variables with a skewed distribution. Survival analysis of the four subgroups classified by the presence of CAD and carotid plaque was performed using Kaplan-Meier analysis for the probability distribution of time to endpoints, and comparisons between each group were made using the log-rank test. Cox proportional hazards regression analysis was performed for multivariable adjustment. To predict concomitant CAD or the presence of carotid plaques, binary logistic regression analyses were performed. To evaluate the
degree of contribution to CAD or carotid plaque, receiver operating characteristic (ROC) analysis was performed using several variables, including clinical risk factors, blood laboratory findings, carotid ultrasound and Doppler indexes, and peripheral tonometry-based indexes. Clinical risk factors included age; sex; presence of hypertension, diabetes, and dyslipidemia; and smoking status. Blood laboratory parameters included LDL-cholesterol level, HDL-cholesterol level, and eGFR. Carotid ultrasound-based indexes included the presence of carotid plaque, extent of carotid plaque, and strongest carotid Doppler index. Peripheral tonometry indexes included baPWV and ABI. To evaluate incremental values in carotid Doppler indexes or arterial stiffness index to traditional risk factors, carotid IMT, and plaque, areas under the curve (AUCs) were compared to those of a previous model. For ROC comparisons between models, MedCal software (version 18.11.3, Broekstraat, Mariakerke, Belgium) was used. All statistical analyses were performed with SPSS 25 (IBM Corp., Armonk, NY, USA), and a two-sided P value of <0.05 was considered significant.

Results

Baseline characteristics: Among the 5,022 consecutive patients, 1,741 (34.5%) patients had a discrepancy between carotid artery plaque and CAD. Comparisons of baseline characteristics between each group are shown in Table I. Overall, FRS increased in a stepwise manner from group I (n = 1,822, 36.3%) to IV (n = 1,459, 29.1%). Group III (n = 863, 17.2%) had a significantly higher FRS than group II (n = 878, 17.5%). Among the groups, group IV patients were the oldest and had the highest prevalence of hypertension, dyslipidemia, diabetes, atrial fibrillation, HF, and CVA history (P < 0.001). They also had a higher LVMi, LAVi, and E/e′ with lower LVEF and showed the lowest levels of common carotid artery end-diastolic velocity (CCA-EDV) and ABI and the highest level of baPWV (P < 0.001). When comparing groups II and III, we noted that patients in group III were older and that more had hypertension, diabetes, HF, atrial fibrillation, and CVA history. Group II comprised more men, more smokers, and more myocardial infarction patients with a lower LVEF, whereas group III patients had a lower CCA-EDV and higher baPWV.

Prognosis of the subgroups according to CAD and carotid plaque: During the follow-up period (median, 1,370 days; interquartile range, 960-1,700 days), 88 (2.3%) patients died of any causes: 114 (3.0%) patients died of any causes: 114 (3.0%) patients had newly developed CV events, including acute myocardial infarction, unstable angina, and death from all CV events; 96 (2.5%) had cerebral infarction; and 33 (0.9%) had HF admission. Patients with carotid plaque had significantly higher all-cause mortality and HF admission rates than those with CAD (all, P < 0.001). New-onset CVA also occurred more often in patients with any carotid plaque than in those with CAD, although the difference was not statistically significant. Most CV events occurred in group IV, followed by group II, III, and I, in a stepwise manner (P < 0.0001). However, regarding HF admission, CVA, and all-cause mortality, group III had worse prognosis than group II. The extent of carotid plaque (none, single side, and both sides) was independently related to HF admission (hazard ratio, 1.67; confidence interval, 1.04-2.68; P = 0.033) after adjusting for age and sex. However, when baPWV was included, the significance was attenuated (P > 0.05). The Kaplan-Meier survival curves for clinical outcomes are presented in Figure 2.

Factors associated with CAD in patients without carotid plaque: In patients without carotid plaque, male sex, older age, smoking history, dyslipidemia, lower HDL-cholesterol level, and lower CCA-EDV were independently related to the presence of CAD (Table II, left). In patients with carotid plaque, smoking history, diabetes, higher E/e′, and lower CCA-EDV were independently related to CAD (all, P < 0.05).

Factors associated with carotid plaque in patients without CAD: In patients without CAD, male sex and
older age were independently related to the presence of carotid plaque (Table II, right), whereas smoking history, hypertension, diabetes, higher E/e' and baPWV, and lower CCA-EDV were independently related to the presence of carotid plaque in patients with CAD (Table II, right). In men, older age and higher baPWV were independently related to the presence of carotid plaque. In women, older age and hypertension were independently related (Supplementary Table, left). A lower HDL level and higher baPWV were independently related to the presence of carotid plaque in younger patients (Supplementary Table, right).

**Incremental predictive value of carotid ultrasound and peripheral tonometry indexes:** The nested clinical risk factors provided a better prediction model (AUC, 0.737) than the FRS (AUC, 0.682; P < 0.001) for detecting CAD. Average IMT, the presence of plaque, extent of carotid plaques, and CCA-EDV could improve the predictive value of FRS (all, P < 0.001) for detecting CAD. When ABI (AUC, 0.712) and nested clinical risk factors (AUC, 0.743) were better than the presence of plaque. When ABI (AUC, 0.712) and nested clinical risk factors (AUC, 0.743) were better than the presence of plaque. When ABI (AUC, 0.712) and nested clinical risk factors (AUC, 0.743) were better than the presence of plaque. When ABI (AUC, 0.712) and nested clinical risk factors (AUC, 0.743) were better than the presence of plaque. When ABI (AUC, 0.712) and nested clinical risk factors (AUC, 0.743) were better than the presence of plaque. When ABI (AUC, 0.712) and nested clinical risk factors (AUC, 0.743) were better than the presence of plaque.
Figure 2. Kaplan-Meier curves for clinical outcomes in each study group. Analyses of event-free survival for each endpoint: composite of cardiovascular events (A), hospitalization for heart failure (B), cerebrovascular accident (infarction) (C), and death from any cause (D). Comparisons between each group were performed using the log-rank test.

Table II. Multiple Binary Regression Analysis of Independent Relationships between the Presence of Coronary Artery Disease or Carotid Plaque within Subgroups

| Variable             | In patients without carotid plaque | In patients with carotid plaque | In patients without CAD | In patients with CAD |
|----------------------|------------------------------------|---------------------------------|------------------------|---------------------|
|                      | OR (95% CI)                        | P                               | OR (95% CI)            | P                   |
| Age, per year        | 1.03 (1.01-1.04)                   | 0.002                           | 1.07 (1.05-1.09)       | < 0.001             | 1.07 (1.05-1.08)   | < 0.001             |
| Male sex             | 1.71 (1.20-2.41)                   | 0.003                           | 1.75 (1.17-2.62)       | 0.006               |                     |                     |
| Smoking history      | 1.58 (1.13-2.20)                   | 0.008                           | 1.50 (1.07-2.09)       | 0.018               | 1.54 (1.13-2.08)   | 0.006               |
| Hypertension         | 1.64 (1.27-2.11)                   | 0.001                           |                       |                     |                     |                     |
| Dyslipidemia         | 1.55 (1.13-2.12)                   | 0.007                           |                       |                     |                     |                     |
| Diabetes             | 1.45 (1.09-1.92)                   | 0.011                           | 1.65 (1.27-2.14)       | < 0.001             |                     |                     |
| HDL-C, per mg/dL     | 0.97 (0.96-0.98)                   | < 0.001                         |                       |                     |                     |                     |
| E/e′                 | 1.03 (1.00-1.07)                   | 0.030                           | 1.06 (1.02-1.09)       | < 0.001             |                     |                     |
| baPWV, per cm/second | 0.97 (0.95-0.99)                   | 0.005                           | 0.97 (0.95-0.99)       | 0.008               | 0.98 (0.96-0.999)   | 0.034               |
| CCA-EDV, per cm/second | 0.97 (0.95-0.99)            | 0.005                           | 0.97 (0.95-0.99)       | 0.008               | 0.98 (0.96-0.999)   | 0.034               |

CAD indicates coronary artery disease; OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; baPWV, brachial-ankle pulse wave velocity; and CCA-EDV, common carotid artery end-diastolic velocity.
ABI and baPWV (AUC, 0.754; \( P < 0.0001 \)) were added to the FRS or nested clinical risk factors, the predictive value was significantly improved (Figure 3A, B).

**Inter-test reliability:** The average intraclass correlation coefficient of CCA-IMT was 0.945 (\( P = 0.008 \)), that of CCA-PSV was 0.854 (\( P = 0.044 \)), and that of CCA-EDV was 0.901 (\( P = 0.023 \)).

**Discussion**

**Differences in contributions to CAD and carotid plaque formation:** In patients without carotid plaque, a lower HDL-cholesterol level, smoking history, and male sex were independently related to CAD development, suggesting that those are more coronary artery-specific risk factors than carotid atherosclerosis. Previous studies have shown that smoking causes impaired lipid metabolism in men and induces endothelial dysfunction, inflammation, vasomotor dysfunction, atherogenesis, and the progression of plaque exclusively in the coronary artery system.\(^{12}\) Research has also indicated that smoking is related to a high triglyceride/HDL ratio with insulin resistance as a potential mechanism of CV events.\(^{13}\) In our study, HDL levels were significantly lower in current smokers and quitters than in never smokers (41.9 ± 10.8 versus 42.8 ± 11.2 versus 45.9 ± 11.8 mg/dL, \( P < 0.001 \)), which supports this potential mechanism.

According to our study results, the presence of any carotid plaque was independently related to increased baPWV and IMT in patients without CAD, especially in male patients in the subgroup analysis, suggesting that carotid plaque would arise differentially to coronary plaque as a process of both atherosclerosis and arteriosclerosis. Additionally, in this group, the effects of smoking and lower HDL-cholesterol level were weaker than in the isolated CAD group. Therefore, carotid plaque may be an index of not only atherosclerosis but also of arterial stiffness, which was also supported by the results of the present study, which showed that the extent of carotid plaque was significantly correlated with age, baPWV, and IMT. As shown in our study results, a lower CCA-EDV, an index of wall shear stress, in combination with increased IMT and arterial stiffness, significantly contributed to carotid plaque formation, usually in the proximal to carotid bifurcation area.\(^{14,15}\) Regarding the wall shear stress-related index, CCA-EDV was more closely related with carotid plaque formation than CCA-PSV in this study. A possible explanation for this finding is that CCA-PSV is affected more by LV stroke volume. CCA-EDV, however, is less affected by LV stroke volume; thus, it would represent more of its own carotid flow dynamics according to carotid geometry.\(^{14,15}\) Finally, lower wall shear stress may induce changes in the orientation of endothelial cells, increased endothelial cell permeability, and the release of vasoactive substances, thus promoting atherosclerosis.

The LV end-systolic wall stress and E/e’ were significantly lower in non-CAD patients with carotid plaque (group III) than in patients with both carotid plaque and CAD (group IV). In terms of wall stress, a lower smoking rate would affect endothelial function in combination with a lower LV mass, which would have preventive effects of CAD. This suggests that the preventive effects of non-smoking for atherosclerosis progression are more prominent in CAD than in carotid artery disease. Additionally,
the contribution of each component of FRS or atherosclerotic CV disease risk score would be different between CAD and carotid artery disease. Male sex, smoking, and diabetes mainly contribute to CAD, whereas hypertension and aging are more related to carotid atherosclerosis.

**Carotid plaque reflects arterial stiffness as a potential risk factor for HF:** According to the results of future outcome evaluation, future HF admission was significantly higher in patients with carotid plaque. Both the total carotid plaque group and patients with isolated carotid plaque (group III) experienced more HF admission than patients with isolated CAD (group II). In addition, the extent of carotid plaque was significantly related to HF admission independent of age and sex, suggesting that carotid plaque may be a potential risk factor for future HF. The isolated carotid plaque group had higher prevalences of female sex and older age and higher SBP, pulse pressure, baPWV, E/e’, and LA volume index, which are known risk factors for HF with preserved ejection fraction, than the isolated CAD group. In addition, the relationship between the extent of carotid plaque and HF admission was significantly attenuated after adjusting for baPWV, suggesting that this relationship is primarily mediated by arterial stiffening and vascular-ventricular uncoupling. Therefore, we suggest that carotid plaque could be a potential risk marker of future HF development.

**Clinical implications:** A significant proportion of patients show a discrepancy in carotid and coronary atherosclerosis, suggesting the presence of differential mechanism of atherosclerosis. It suggests that carotid ultrasound is not an enough screening test for detecting pan-vascular atherosclerosis, especially for CAD. Because older or male patients with smoking history, lower HDL-cholesterol level, or lower CCA-EDV were related to CAD in the absence of carotid plaques, an individual diagnostic approach, such as coronary calcium score, would be additionally recommended in patients with coronary-specific risk factors. In addition, this study demonstrated that the presence and extent of carotid plaque were significantly associated to HF admission independent of age and sex. It suggests that patients with carotid plaques, reflecting arterial stiffness, would be benefited by the inhibition of renin-angiotensin-aldosterone system, not just by statin or antiplatelet agents, for prevention of future events.

**Limitations:** First, because the study group was neither hypothesis-driven nor a prospectively enrolled population, there may be some referral bias. Although most patients underwent invasive coronary artery angiography because of chest pain or suspected ischemic heart disease, the enrolled population had a heterogeneous disease status. However, since this study was based on registry data from clinical practice and included a large number of consecutively enrolled patients, the effects of that bias would be low. Second, because baPWV and ABI were evaluated in 71% of patients and carotid Doppler in 73% of patients, the results of multivariable analysis can be applied to the subgroups; however, since the number of patients was high enough and there was no significant systematic bias, the results can be applied to the whole study population. Third, our carotid ultrasonography protocol traces atherosclerotic plaque in the whole CCA, ECA, ICA, and vertebral artery with Doppler evaluation; therefore, it is possible that atheromatous plaques in the intracranial distal ICA were undetected. Lastly, we did not analyze the quantitative extent and amount of plaque in the coronary and carotid arteries; therefore, in patients with carotid atherosclerosis or CAD, the degree of atherosclerosis would be heterogeneous.

**Conclusions**

A significant proportion of patients show a discrepancy in carotid and coronary atherosclerosis. Further investigations to identify differential pathogenesis and to establish a tailored treatment for coronary and carotid atherosclerosis are warranted. Thus, even in patients without carotid plaques, additional coronary evaluation, such as computed tomographic calcium score, would be helpful in patients with older age, male sex, smoking habits, lower HDL level, or lower CCA-EDV. In addition, the extent of carotid plaque would be a potential risk marker for HF through arterial stiffness.

**Disclosure**

**Conflicts of interest:** None.

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Supplemental Files

Supplemental Table

Please see supplemental files; https://doi.org/10.1536/ihj.20-318