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# Incremental value of carotid intraplaque hemorrhage for discriminating prior coronary events

Jie Sun<sup>1\*</sup>, Daniel S. Hippe<sup>1</sup>, Hunter R. Underhill<sup>2</sup>, Baocheng Chu<sup>1</sup>, Tobias Saam<sup>3</sup>, Norihide Takaya<sup>4</sup>, Jianming Cai<sup>5</sup>, Minako Oikawa-Wakayama<sup>6</sup>, Wei Yu<sup>7</sup>, Li Dong<sup>7</sup>, Chun Yuan<sup>1</sup> and Thomas S. Hatsukami<sup>8\*</sup>

## Abstract

**Background:** The value of noninvasive assessment of carotid plaque composition in identifying patients with high coronary risk remains elusive. We sought to determine whether and which carotid plaque components are associated with prior coronary events independent of traditional risk factors and plaque burden.

**Methods:** Asymptomatic subjects with 50–79 % carotid stenosis by ultrasound were imaged with a multi-contrast carotid MRI protocol at 1.5 T. The independent associations between plaque components (fibrous tissue, calcification, lipid-rich necrotic core [LRNC] and intraplaque hemorrhage [IPH]) and prior coronary events, including myocardial infarction and coronary revascularization, were evaluated by controlling for traditional risk factors and plaque burden metrics.

**Results:** A total of 159 subjects ( $69.7 \pm 9.0$  years, 84 % males) were included. Prior coronary events were documented in 66 (42 %) subjects, and were associated with a larger carotid plaque burden consisting of more LRNC and calcification. Additionally, a higher prevalence of IPH was observed in subjects with prior coronary events (32 % vs. 15 %,  $p = 0.019$ ). In multivariate analysis, the percent wall volume was an independent discriminator among plaque burden metrics after accounting for traditional risk factors (odds ratio per 1-SD increase: 1.7 [1.2, 2.6]); the presence of IPH remained as a significant discriminator after accounting for traditional risk factors and percent wall volume (odds ratio: 2.9 [1.1, 7.6]) while other compositional metrics did not.

**Conclusions:** IPH in the carotid artery was independently associated with prior coronary events. IPH imaging may provide incremental information on patients' coronary risk beyond traditional risk factors and carotid plaque burden assessment.

**Keywords:** Carotid artery, Coronary artery disease, Intraplaque hemorrhage, Magnetic resonance imaging

## Background

Because of the systemic nature of atherosclerosis, sub-clinical carotid disease has long been used as a surrogate of coronary artery disease (CAD). Measurements on carotid plaque burden have been shown to predict the extent and clinical risk of underlying CAD [1–4], whereas the value of carotid plaque composition, although widely believed to indicate lesion instability, remains elusive for the evaluation of CAD risk.

Assessment of carotid plaque composition has been available via noninvasive imaging, which potentially can provide clinicians with incremental information on patients' coronary risk. Recently, the echolucent carotid plaques by ultrasound [5] and those with high-intensity signals by T1-weighted magnetic resonance imaging (MRI) [6] were shown to predict future coronary events independent of clinical risk factors. However, compositional features are known to have positive relationships with plaque burden [7, 8], and their added value will not be clear unless tested against plaque morphological metrics.

In this study, we sought to test whether and which carotid plaque compositional metrics confer incremental values for discriminating prior coronary events in

\* Correspondence: sunjie@u.washington.edu; tomhat@u.washington.edu

<sup>1</sup>Department of Radiology, University of Washington, 850 Republican St, WA, Seattle 98109, USA

<sup>8</sup>Department of Surgery, University of Washington, 850 Republican St, WA, Seattle 98109, USA

Full list of author information is available at the end of the article

subjects with subclinical carotid disease. While all subjects in this study had imaging evidence of atherosclerosis, those with prior coronary events were considered to be at a much higher risk for future events [9]. We hypothesized that specific markers on carotid plaque composition could help identify subjects with prior coronary events and thus serve as novel markers for vulnerable patients. Carotid MRI provides comprehensive plaque morphological measurements, and is a validated tool for detecting major plaque components in vivo [10–12].

## Methods

### Study population

Subjects in a previously-established cohort were included in this retrospective study [13]. Briefly, asymptomatic subjects with substantial carotid plaques were recruited in this exploratory study to include a wide spectrum of compositional phenotypes. Specific criteria were: 1) 50–79 % stenosis by duplex ultrasound in at least one carotid artery; 2) neurologically asymptomatic defined as no cerebrovascular symptoms in the 6 months prior to enrollment; 3) no prior carotid endarterectomy (CEA), neck radiation or contraindications for MRI (e.g. metal implants, claustrophobia). Enrolled subjects completed a standardized health questionnaire covering demographics and cardiovascular risk factors (smoking, hypertension, hypercholesterolemia, and diabetes mellitus) [13]. Smoking was self-reported and included former smoking and current smoking. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg, or taking anti-hypertensive agents. Diabetes was defined as previously confirmed diagnosis and/or use of anti-diabetic agents. Hypercholesterolemia was defined as a history of total cholesterol  $> 5$  mmol/l and/or low-density lipoprotein cholesterol (LDL-C)  $> 3$  mmol/l, or taking lipid-lowering medications. Prior coronary events were collected and verified by chart review. A positive history of coronary events was defined as having one or more of the following events: 1) hospitalization for myocardial infarction; 2) coronary revascularization including angioplasty, stenting and coronary artery bypass graft (CABG). All study procedures were reviewed and approved by the institutional review board. Subjects provided informed consent before enrollment.

### MRI Protocol

All scans were performed on a 1.5 T scanner (Signa Horizon EchoSpeed, GE Healthcare, Milwaukee, Wisconsin, USA) using phased-array surface coils (Pathway, Seattle, Washington, USA). A previously published standardized protocol [14, 15] was used to acquire cross-sectional, multi-contrast images (3-dimensional time-of-flight [TOF], T1-weighted, proton density-weighted [PD], and T2-

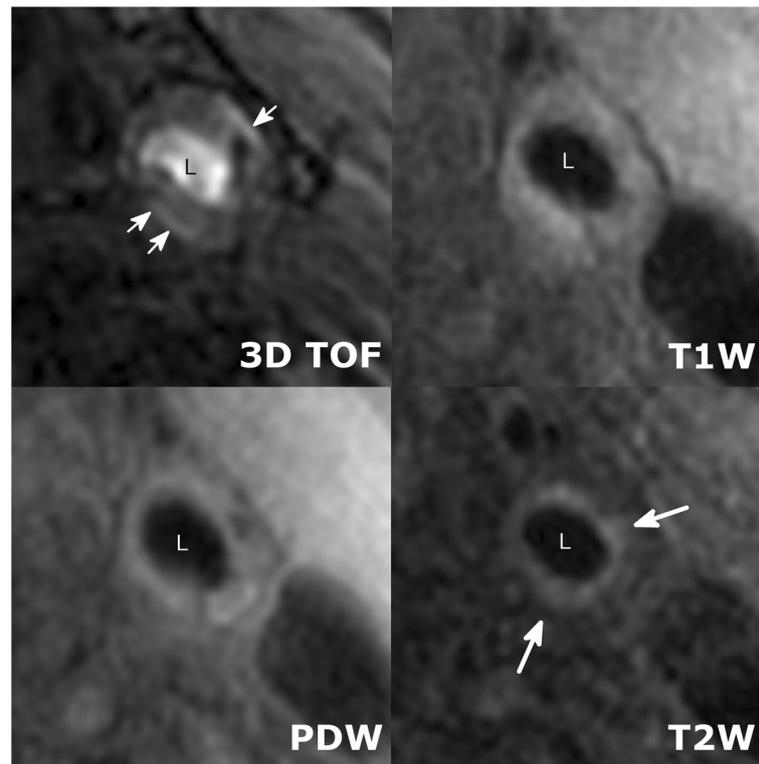
weighted) that were centered at the carotid bifurcation of the side with 50–79 % stenosis. No contrast agent was used to increase patient recruitment and compliance. Previous studies have shown that this non-contrast protocol was able to characterize major plaque components [10, 13]. All images were obtained with field-of-view of 13 to 16 cm, matrix size of  $256 \times 256$ , and slice thickness of 2 mm. Scan coverage was 40 mm for TOF, 20–24 mm for T1-weighted, and 30 mm for proton density-weighted and T2-weighted sequences. Total acquisition time was approximately 30 min.

### Image analysis

Eight reviewers with at least 1-year experience in MR plaque imaging participated in image analysis while blinded to clinical data using a custom-designed image analysis software package (CASCADE, University of Washington, Seattle, Washington, USA) [16]. Only the index artery, defined as the side with 50–70 % stenosis by ultrasound, was analyzed. The four contrast weightings (TOF, T1, PD, and T2) were registered using the carotid bifurcation as a landmark. Lumen and outer wall boundaries were outlined on each cross-sectional slice as well as plaque components that were determined using previous published criteria (Figure 1) [10, 12]. Briefly, calcification appears hypointense on all weightings; intraplaque hemorrhage (IPH) appears hyperintense on TOF and T1-weighted images; lipid-rich necrotic core (LRNC) usually appears hypointense on T2- and PD-weighted images but may have variations if it contains IPH [12]. Remaining wall areas were classified as fibrous tissue. Subsequently, maximum wall thickness, maximum percent wall area ( $100 \% \times \text{wall area}/\text{total vessel area}$ ), percent wall volume ( $100 \% \times \text{wall volume}/\text{total vessel volume}$ ), were calculated. Percent volumes of calcification and LRNC and the presence/absence of IPH were also calculated and/or recorded. All imaging data were based on consensus opinion of at least two reviewers.

### Statistical analysis

All data are presented as mean  $\pm$  standard deviation (SD) for continuous variables and count with percentage for categorical variables. Subjects were stratified according to a positive or negative history of prior coronary events. Clinical and imaging characteristics were compared between the two groups using the independent *t*-test, Mann–Whitney test, and Fisher's exact test, as appropriate. The incremental values of: 1) carotid plaque morphological metrics over clinical variables; and 2) compositional metrics over clinical variables and morphological metrics, for discriminating prior coronary events, were examined using multivariate logistic regression analysis and presented as odds ratios (OR) with 95 % confidence interval (CI). To examine the influence of plaque burden on the ability of



**Fig. 1** Carotid plaque burden and composition detected by combined use of multiple MR weightings at 1.5 T. Arrows indicate lipid-rich necrotic core as hypointense areas on T2W images. Arrowheads indicate intraplaque hemorrhage as hyperintense areas on TOF images. PDW = proton-density-weighted; T1W = T1-weighted; T2W = T2-weighted; TOF = time-of-flight

compositional metrics for discriminating prior coronary events, interactions between plaque morphological and compositional metrics were also tested. All data analyses were performed using R 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as  $P < 0.05$ .

## Results

### Clinical and imaging characteristics

Table 1 summarizes the clinical and imaging characteristics of the study population ( $N = 159$ ). Prior coronary events were documented in 66 (42 %) subjects. Compared to subjects without prior coronary events, those with prior coronary events had a higher prevalence of hypercholesterolemia (92 % vs. 70 %,  $p = 0.001$ ), and were more frequently on statin therapy (82 % vs. 52 %,  $p < 0.001$ ), but otherwise had similar clinical profiles (Table 1). Observed differences in carotid plaques included larger plaques, less fibrous tissue, and a higher prevalence of IPH in subjects with prior coronary events (Table 1).

### Incremental value of carotid plaque morphology

All three morphological metrics of plaque burden were significantly associated with prior coronary events (Table 2).

**Table 1** Clinical and imaging characteristics stratified by history of prior coronary events

	Negative ( $n = 93$ )	Positive ( $n = 66$ )	$p$ value
Clinical characteristics			
Age, years	69.3 ± 8.9	70.2 ± 9.2	0.52
Male sex	75 (81)	59 (89)	0.19
Smoker	79 (85)	61 (92)	0.22
Hypertension	68 (73)	54 (82)	0.25
Hypercholesterolemia	65 (70)	61 (92)	0.001
Diabetes mellitus	25 (27)	18 (27)	0.99
Statin use	48 (52)	54 (82)	<0.001
Imaging characteristics			
Maximum wall thickness, mm	4.1 ± 1.4	4.6 ± 1.7	0.035
Maximum percent wall area	71.5 ± 13.4	76.0 ± 11.0	0.028
Percent wall volume	60.2 ± 10.1	65.4 ± 8.9	0.003
% calcification	3.9 ± 5.0	5.5 ± 6.5	0.098
% lipid-rich necrotic core	9.2 ± 11.1	12.8 ± 12.6	0.13
% fibrous tissue	84.6 ± 11.0	78.7 ± 11.9	0.003
Presence of IPH	14 (15)	21 (32)	0.019

Data are presented as mean ± SD or count (percentage)

% = percent volume; IPH = intraplaque hemorrhage; SD = standard deviation

**Table 2** Associations between carotid plaque morphological metrics and prior coronary events

	Unadjusted		Adjusted <sup>b</sup>	
	OR (95 % CI) <sup>a</sup>	<i>p</i> value	OR (95 % CI) <sup>a</sup>	<i>p</i> value
Maximum wall thickness	1.4 (1.0, 2.0)	0.034	1.4 (1.0, 2.0)	0.092
Maximum percent wall area	1.4 (1.0, 2.0)	0.030	1.4 (0.9, 1.9)	0.105
Percent wall volume	1.8 (1.2, 2.5)	0.002	1.7 (1.2, 2.6)	0.005

<sup>a</sup>Data are presented as odds ratios per 1-SD higher values

<sup>b</sup>Adjusted for clinical risk factors (age, gender, smoking status, hypertension, hypercholesterolemia, diabetes mellitus and statin use)  
CI = confidence interval; OR = odds ratio; SD = standard deviation

The OR for prior coronary events ranged from 1.4 to 1.8 per 1-SD increase in maximum wall thickness, maximum percent wall area, and percent wall volume. Percent wall volume not only appeared to be the strongest discriminator amongst the plaque morphological metrics for prior coronary events, but also remained significant after adjusting for demographics and clinical risk factors (OR: 1.7 [1.2, 2.6] per 1-SD increase,  $p = 0.005$ ).

#### Incremental value of carotid plaque composition

Among carotid plaque compositional metrics, a lower percent volume of fibrous tissue and presence of IPH were associated with a positive history of coronary events (Table 3). After adjusting for clinical risk factors, as well as percent wall volume, the presence of IPH remained as a significant discriminator for prior coronary events (OR: 2.9 [1.1, 7.6],  $p = 0.033$ ).

Plaque burden did not appear to influence the ability of IPH to discriminate subjects with prior coronary events ( $p$ -value ranged from 0.40 to 0.99 for interactions). Fig. 2 shows the association between IPH and prior coronary events in different subgroups defined by carotid plaque morphological metrics. Of note, all subjects in the lower half of maximum wall thickness and with IPH had prior coronary events.

#### Discussion

By using carotid MRI, we were able to evaluate and compare carotid plaque morphological and compositional metrics in relation to coronary plaque vulnerability, defined as having prior coronary events in this study. The most pronounced difference in carotid plaque morphology between subjects with and without prior coronary events was shown in percent wall volume. Furthermore, the incremental value of carotid plaque composition for discriminating prior coronary events, specifically the presence of IPH, was demonstrated by accounting for clinical risk factors as well as percent wall volume. In addition to some pathophysiological insights, our findings indicate that a combination of three-dimensional plaque characterization and IPH detection in the assessment of subclinical carotid atherosclerosis may offer the most promising information on patients' coronary risk.

Carotid plaque detection by B-mode ultrasound has been shown to improve individual risk assessment compared to the intima-media thickness [4]. The introduction of novel ultrasound techniques provides additional opportunities to optimize this approach through improved plaque characterization [17, 18]. This concept is further supported by autopsy findings showing that vulnerable features tend to be present at multiple arterial beds within the same individual [19, 20]. To determine what information embedded in carotid plaque tissue composition are relevant to coronary risk, we used carotid MRI to compare carotid plaque compositional metrics between subjects with and without prior coronary events. Carotid MRI gives a comprehensive assessment of local plaque burden by capturing both luminal stenosis and outward remodeling. Additionally, combining MRI contrast weightings has been shown to be able to characterize plaque components [10, 11]. Therefore, multiple morphological and compositional metrics can be compared head-to-head in a single study.

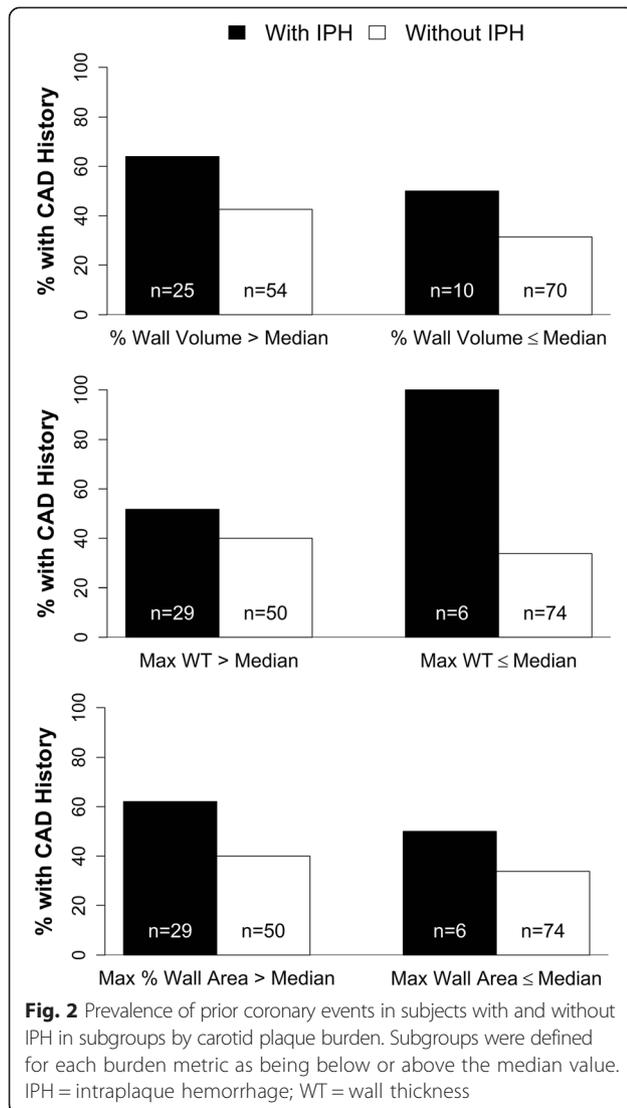
The presence of IPH in the carotid artery was found to be an additional indicator for coronary vulnerability, with an odds ratio of 2.9 (95 % CI: 1.1-7.6) for prior coronary events after adjustment for clinical variables and percent wall volume. The observation is consistent with a previous histopathological study by Hellings et al. [21] in which carotid IPH identified by post-surgical examination of carotid endarterectomy specimens was associated with systemic cardiovascular outcomes. It was noted that the observed relationship between carotid IPH and

**Table 3** Associations between carotid plaque compositional metrics and prior coronary events

	Unadjusted		Adjusted <sup>b</sup>	
	OR (95 % CI) <sup>a</sup>	<i>p</i> value	OR (95 % CI) <sup>a</sup>	<i>p</i> value
% calcification	1.3 (1.0, 1.8)	0.083	1.2 (0.8, 1.7)	0.40
% LRNC	1.4 (1.0, 1.9)	0.052	1.2 (0.8, 1.8)	0.40
% fibrous tissue	0.6 (0.4, 0.8)	0.002	0.7 (0.4, 1.1)	0.13
Presence of IPH	2.6 (1.2, 5.7)	0.014	2.9 (1.1, 7.6)	0.033

<sup>a</sup>Data are presented as odds ratios per 1-SD higher values for continuous variables

<sup>b</sup>Adjusted for age, gender, smoking status, hypertension, hypercholesterolemia, diabetes mellitus, statin use and percent wall volume  
% = percent volume; CI = confidence interval; IPH = intraplaque hemorrhage; OR = odds ratio; SD = standard deviation



coronary events alone was more marginal (hazard ratio: 1.6, 95 % CI: 0.9-3.0) [21]. Surgical patients have end-stage plaques and are frequently symptomatic whereas our study included only asymptomatic subjects with moderate carotid disease. After stratifying our study population by plaque size, there appeared to be no evidence that the relationship between IPH and prior coronary events varied in those with high or low plaque burden. Nonetheless, subjects with IPH but not much wall thickening may represent a unique group for further investigations (Fig. 2). Collectively, existing evidence suggests clinicians to note the increased coronary risk if IPH is detected in the carotid artery, particularly in those with asymptomatic carotid lesions.

In contrast to IPH, other plaque components did not show incremental discriminative power over plaque morphological assessment. Subjects with prior coronary events had significantly less fibrous tissue in the carotid plaque,

due to increase in both calcification and lipid core. However, such an association was largely accounted for by clinical risk factors and concomitantly larger percent wall volume.

Natural history studies have revealed that most coronary events were preceded by rapid plaque expansion that was unusual and unrelated to baseline plaque burden [22–24]. IPH, with the capability to induce changes in plaque behavior [25], may play a critical role in the pathogenesis of coronary events. In a postmortem study, Fleiner et al. described that the hyperplasia of vasa vasorum was a systemic feature of symptomatic patients [20]. As adventitial vasa vasorum is a major source of IPH [26], the finding by Fleiner et al. supports the conjecture that carotid IPH indicates increased probability of coronary IPH. Another study by Moreno et al. also sheds light by showing that genotypes related to hemoglobin clearance may determine one's susceptibility to IPH-induced detrimental effects [27]. It is possible that the presence of carotid IPH by MRI indicates certain genetic vulnerabilities related to IPH metabolism. Nonetheless, given the limited understanding of the pathophysiology of IPH in the current literature, although IPH in the carotid artery appears to indicate additional systemic factors that contribute to plaque instability, the exact mechanisms remain to be investigated.

Singh et al. [28] also noted a higher prevalence of carotid IPH in patients with prior coronary events. That study included subjects referred for carotid MRI due to suspected neurovascular disease, so the study population appears to be a mixture of symptomatic and asymptomatic subjects. It is conceivable that there would be a wider range of carotid plaque burden in the previous report compared to the present data. As IPH is known to be associated with a larger plaque burden [29], a wider range of plaque burden in study population makes it difficult to argue that the observed relationship is not due to the higher plaque burden associated with IPH but related to the unique pathophysiology of IPH. In the present study, by including subjects with similar extent of carotid disease and quantifying plaque burden in a three-dimensional fashion, we were able to test the independent association between carotid IPH and coronary events rigorously. In this study, plaque morphological measurements were derived from MRI rather than ultrasound which is more widely used in clinical practice. However, MRI provides multiple plaque morphological metrics, and therefore the incremental value of carotid plaque composition could be rigorously tested. The maximum wall thickness measures plaque burden at a single location. The maximum percent wall area measures a single slice and essentially indicates luminal narrowing after taking into account outward remodeling, which is similar to stenosis measurement on black-blood carotid MRI proposed by Babiarz et al. [30]. The percent wall volume, as a

3-dimensional metric, is similar to the percent atheroma volume that is used in intravascular ultrasound studies of coronary vasculature [31]. Among the three morphological metrics, the percent wall volume was the best discriminator for prior coronary events, supporting the pursuit of 3-dimensional carotid plaque characterization as a future tool in CAD management [32].

### Implications

Findings from this study have implications both for understanding the pathophysiology of vulnerable patients and for optimizing clinical management in individuals. Although atherosclerosis becomes highly prevalent as people get older, certain patients are at a particular high risk for clinical events. Our data suggest that carotid IPH was associated with increased risk for coronary events and the association was not explained by differences in traditional risk factors and plaque burden. Thus, it is conceivable that additional systemic factors that relate to the pathogenesis of IPH may be the underlying players, such as the hyperplasia of vasa vasorum and haptoglobin genotype [20, 27]. Accordingly, there is potential for using carotid IPH as a novel marker for high coronary risk in developing medical treatment strategies, which may include more stringent treatment goals for lipid-lowering and anti-hypertensive agents as well as novel agents that can target IPH and its detrimental effects on plaque progression.

### Study limitations

There are several limitations of the present study. Our study population is selective in that it only included neurologically asymptomatic subjects with 50-79 % carotid stenosis by ultrasound. Despite the relatively narrow range in stenosis, a wide range in plaque composition was observed and offered a good opportunity to test the incremental value of plaque composition in discriminating prior coronary events. However, it remains to be seen whether the independent association of IPH with coronary events applies to the general population. Due to the retrospective nature of the design, patients with severe coronary events such as coronary death could not be included. We do not expect this selection bias that is present in most clinical research to affect our study findings. But the prevalence of carotid IPH in those with more severe coronary events could be higher than what was seen in this study. In addition, circulating biomarkers, such as C-reactive protein, which have been shown to improve risk appraisal in individuals [33], were not examined in the present study. Therefore, we could not exclude the possibility that the association between IPH and coronary events may be mediated by biomarkers. It is worth mentioning that epidemiological studies using carotid MRI are still sparse, and no biomarkers have been linked with IPH to date.

### Conclusions

In conclusion, subjects with prior coronary events had a high prevalence of IPH. The association could not be explained by differences in traditional risk factors and plaque burden. IPH may provide incremental information on patients' coronary risk, possibly by indicating additional systemic factors that contribute to plaque instability.

### Competing interests

DSH reports grants from GE Healthcare and Philips Healthcare. CY receives research grants from the NIH and Philips Healthcare, and serves as a Member of Radiology Advisory Network, Philips. TSH receives research grants from the NIH and Philips Healthcare. The other authors declare that they have no competing interests.

### Authors' contributions

JS performed the design of the study, analyzed the data, interpreted the data, and drafted the manuscript. DSH participated in study design, contributed to statistical analysis, data interpretation, and revised the manuscript. HRU, BC, TS, NT, JC, MW, WY, LD participated in image analysis, data interpretation, and manuscript revision. CY assisted in the study design, data interpretation, and manuscript revision. TSH carried out the design of the study, interpreted the data and revised the manuscript. All authors read and approved the final manuscript.

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None.

### Author details

<sup>1</sup>Department of Radiology, University of Washington, 850 Republican St, WA, Seattle 98109, USA. <sup>2</sup>Department of Pediatrics, University of Utah, Salt Lake City, UT, USA. <sup>3</sup>Institute for Clinical Radiology, Ludwig-Maximilians-University Hospital Munich, Munich, Germany. <sup>4</sup>Department of Cardiology, Juntendo University, Tokyo, Japan. <sup>5</sup>Department of Radiology, PLA General Hospital, Beijing, China. <sup>6</sup>Department of Radiology, Japanese Red Cross Sendai Hospital, Sendai, Japan. <sup>7</sup>Department of Radiology, Beijing Anzhen Hospital, Beijing, China. <sup>8</sup>Department of Surgery, University of Washington, 850 Republican St, WA, Seattle 98109, USA.

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