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Prediction of High-Risk Plaque Development and Plaque Progression with the Carotid Atherosclerosis Score: A Prospective MRI Study

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Abstract

Objectives—The aim of this prospective study was to evaluate the Carotid Atherosclerosis Score (CAS) for predicting the development of high-risk plaque features and plaque burden progression.

Background—Prior studies have shown that carotid intraplaque hemorrhage (IPH) and a disrupted luminal surface (DLS), as identified by magnetic resonance imaging (MRI), are associated with greater risk for cerebrovascular events. Based on data from a large cross-sectional study, a scoring system was developed to determine which plaque features are associated with the presence of IPH and DLS. However, the predictive value of CAS has not been previously tested in a prospective, longitudinal study.

Methods—120 asymptomatic subjects with 50-79% carotid stenosis underwent carotid MRI scans at baseline and three-years thereafter. Presence of IPH and DLS, wall volume, maximum wall thickness, and maximum percent lipid-rich necrotic core area were measured at both time points. Baseline CAS values were calculated based on previously published criteria.

Results—Of the 73 subjects without IPH or DLS at baseline, nine (12%) developed one or both of these features during follow-up. There was a significant increasing trend between CAS and the

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development of new DLS (p<0.001) and with plaque burden progression (p=0.03), but not with the development of new IPH (p=0.3). Percent carotid stenosis was not significantly associated with new DLS (p=0.2), new IPH (p=0.1) or plaque progression (p=0.6)..

Conclusion—CAS was found to have a significant increasing relationship with incident DLS and plaque progression in this prospective study. CAS can potentially provide improved risk stratification beyond luminal stenosis.

Keywords

Carotid Atherosclerosis Score; Stenosis; Plaque progression; Disrupted Luminal Surface

Introduction

Stroke is one of the leading causes of mortality and morbidity worldwide, and carotid atherosclerotic disease is a primary etiologic factor.(1,2) Currently, the risk of stroke associated with carotid atherosclerosis is stratified by the severity of luminal stenosis.(3) Several large prospective clinical trials (4-6) have supported intervention with carotid endarterectomy (CEA) or stenting for symptomatic patients with >70% stenosis to reduce stroke risk. However, for symptomatic patients with <70% stenosis and for asymptomatic patients, stenosis alone may not be a reliable measure of stroke risk. A growing body of evidence suggests that plaque composition, as detected by MRI, rather than luminal narrowing, is the critical factor governing risk of ischemic cerebrovascular events originating from the carotid artery. (7-12) Specifically, the presence of a disrupted luminal surface (e.g. fibrous cap rupture (FCR) or ulceration) and/or intraplaque hemorrhage is indicative of a high risk lesion for ischemic events. (13-16) While results from studies to better characterize carotid atherosclerosis using MRI hold great promise, progress toward its translation to clinical practice has been hindered by the complex nature of analysis of the multi-contrast weighted images. A simple-to-use method to classify plaque that has predictive value for carotid lesion progression and future ischemic events is essential to move the field forward.

In a cross-sectional study of 435 subjects collected from four imaging sites in the United States and China, Underhill et al.(17) proposed a rapid risk stratification strategy, known as CAS, based on maximum wall thickness (WT) and the maximum lipid-rich necrotic core percentage (%LRNC). Statistical analysis showed that CAS was an accurate predictor for the presence of IPH and FCR in the test subgroup of this single time-point study. Furthermore, when compared to stenosis measured by MR angiography (MRA), CAS was a stronger classifier of high-risk features.

Though CAS was successfully designed and tested in a cross-sectional study (17), it is unclear if it can predict the development of high-risk plaque features and plaque burden progression in a prospective, longitudinal study. The aims of the current work were to (i) investigate the associations between the CAS, incident IPH or DLS, and plaque burden progression during follow-up; and (ii) to compare CAS and stenosis in risk prediction amongst asymptomatic individuals with 50-79% carotid stenosis.

Methods

Study Subjects

Individuals with 50-79% carotid stenosis on at least one side consented to be recruited into this study at the University of Washington Medical Center and the Veterans Affairs Puget Sound Health Care Systems. Carotid stenosis was determined with duplex sonography using the Strandness criteria.(18) The side with greater stenosis was defined as the index artery. All subjects were asymptomatic with regard to their carotid disease for the six months prior to recruitment. One hundred twenty (120) subjects underwent a baseline carotid MRI and follow-up scan three years thereafter.

Subjects with any of following conditions were excluded: 1) carotid endarterectomy before or during the study on the index carotid artery; 2) prior radiation therapy to the neck; 3) contraindication to MRI.

MR Imaging

All subjects underwent MR imaging at baseline and at the 3-year follow-up on a 1.5T scanner (Signa, Version 5.8, GE Healthcare, Milwaukee, Wisconsin) with a bilateral 4-element, phased array surface coil (Pathway MRI, Seattle, Washington). A multi-contrast protocol for carotid MR imaging(19) was used to acquire axial images with the parameters listed in Table 1.

Image Analysis

The index arteries of all subjects were interpreted via consensus opinion by two experienced reviewers who received certified training at the Vascular Imaging Lab, University of Washington. Both reviewers were blinded to the time point and clinical information during image analysis. For each scan, multi-contrast MR images were aligned using the carotid bifurcation as a landmark. At each registered axial slice, images were graded for image quality on a four-point scale where 1=poor and 4=excellent. Slices with image quality ≥2 at both time points were interpreted using vascular image analysis software (CASCADE, Vascular Imaging Lab, University of Washington) (20). After drawing the lumen and outer wall boundaries on each slice, plaque burden measurements were derived, including wall area and volume, maximum wall thickness (WT) and mean normalized wall index (NWI). NWI was computed per slice as wall area / (lumen area + wall area). Based on validated analysis criteria, (21,22, 28) IPH, LRNC, FCR, and ulceration were identified. The percent LRNC was also recorded per slice, where %LRNC = 100% × (LRNC area / wall area). Using the carotid bifurcation as a landmark, scans from the two time points were matched and artery-based measurements were computed from the common coverage for each subject. The inter-reader and inter-scan reproducibility of these measurements has been reported in previous studies.(23,24)

The severity of carotid stenosis was quantified based on MRA images rendered from TOF data by a trained reviewer who was blinded to clinical information and cross-sectional carotid MR images. Luminal stenosis was measured on the index side of the carotid artery using the NASCET criterion: 1 – (luminal diameter at the location with maximal narrowing /

luminal diameter of normal distal internal carotid artery) × 100%.(4) All measurements were acquired on Maximum Intensity Projection (MIP) images with CASCADE.

CAS was computed from the max WT and maximum LRNC percentage measurements, where max %LRNC represented the cross-sectional slice with the largest %LRNC value for the index carotid artery. CAS was determined as follows: CAS=1 if max WT ≤ 2 mm, otherwise if max WT > 2 mm, then CAS was set according to max %LRNC; CAS=2 if max %LRNC was <20%, CAS=3 if max %LRNC was between 20% and 40%, and CAS=4 if max %LRNC was >40%.

Statistical Analysis

Plaque variables were aggregated over the slices within each artery, where only slices present in scans at both time points were included. Arteries with less than 10 mm of common coverage were excluded. Patient demographics were summarized using mean ± SD and range for continuous measurements and count (percentages) for categorical variables. The Chi-Squared test for trend was used to test for an increasing association between CAS and new high-risk features.

Plaque progression was defined as the annualized wall volume change between time points. Subjects who developed ulcerations over the follow-up period were excluded from the analysis of plaque progression because morphology measurements (lumen and wall volumes) were confounded by the presence of ulceration. Plaque progression was summarized as mean ± SD for the whole group and for each subgroup defined by the baseline level of CAS. The progression rate was compared to 0 using the one-sample t-test. Linear regression was used to test for an increasing trend between the baseline CAS and plaque progression.

Receiver operating character (ROC) curves and the area-under-the-curve (AUC) statistic were used to summarize the strength of the association between new DLS or IPH and CAS, carotid stenosis and plaque burden—wall volume, mean NWI and max WT. Pearson's correlation coefficient was used similarly with the same predictors and plaque progression as the outcome. All statistical analyses were performed using R (version 2.11.0, R Foundation for Statistical Computing, Vienna, Austria). Throughout, two-tailed tests were used with $p<0.05$ denoting statistically significance.

Results

Out of the 120 subjects recruited, 20 were excluded: 12 with poor image quality at either time-point, seven with insufficient coverage, and one subject who underwent CEA during the study period. To evaluate the association between CAS and incident IPH and DLS, the 73 subjects out of 100 without these features at baseline were analyzed. The mean time interval between baseline and follow-up scans was 3.0 ± 0.2 years. Demographic information and baseline plaque measurements of these 73 subjects are shown in Table 1.

Incidence of New High-Risk Features

The incidence of new DLS or IPH amongst the 73 subjects without these features at baseline is summarized in Table 3. At follow up, 7 subjects developed DLS (including 2 ulcerations) and 4 developed IPH (two of which were coincident with DLS). All new DLS were found in those with CAS=3 or 4 at baseline. There was a significant increasing trend for new DLS with increasing baseline CAS ($p<0.001$) but not with new IPH ($p=0.3$).

Plaque Progression During Follow-Up

Two participants with evidence of new ulceration at follow-up were excluded from the plaque progression analysis (one with baseline CAS=3 and the other with CAS=4). The mean progression rate was 14.6 ± 23.5 mm^3/year ($p<0.001$ for comparison to 0) in the remaining 71 subjects. Figure 2 shows the mean progression rates within the subgroups defined by baseline CAS. There was a significant increasing trend by linear regression ($p=0.03$) between the mean progression rates of 4.7, 13.9, 18.1, and 42.0 mm^3/year and baseline CAS=1, 2, 3 and 4, respectively.

Comparison of CAS, Carotid Stenosis, and Plaque Burden Measurements in Predicting New DLS and IPH

ROC analysis was conducted with new DLS and IPH as outcomes and baseline CAS, stenosis and plaque burden (wall volume, mean NWI and max WT) as predictors (Table 4). CAS had the highest AUC (AUC=0.96 [95% CI: 0.92, 1.0]) among predictors for new DLS while mean NWI and max WT had the highest AUC for predicting new IPH (AUC=0.78, $p > 0.06$ for both). The AUCs for carotid % stenosis were 0.65 ($p=0.2$) and 0.74 ($p=0.1$) for new DLS and IPH, respectively. None of the variables considered were significantly associated with new IPH. When the combined outcome of new DLS or IPH was examined, CAS had the highest AUC (AUC=0.86 [95% CI: 0.71, 1.0]), followed closely by mean NWI (AUC=0.84 [95% CI: 0.70, 0.99]).

Comparison of CAS and Severity of Carotid Stenosis in Predicting Plaque Burden Progression

The correlations between the plaque progression rate and baseline CAS, stenosis and plaque burden are summarized in Table 5. CAS had the highest correlation (r=0.26 [95% CI: 0.03, 0.47]) while % stenosis has the lowest (r=-0.06 [95% CI: −0.29, 0.18]). The three plaque burden measures had similar levels of correlation with progression of $r=0.22 – 0.23$, but there was only a trend towards significance ($p<0.1$ for all three measures).

Discussion

The initial formulation and testing of CAS was based on data from a cross-sectional study (17). The serial carotid MRI study reported herein demonstrates that CAS measures are predictive of future carotid luminal surface disruption, thus providing prospective confirmation of the earlier single time-point study findings. Furthermore, a significant association was noted between CAS and plaque progression in asymptomatic patients with 50-79% stenosis and who do not have carotid DLS or IPH at baseline. We caution the reader against over-interpretation of the data presented given the relatively low number of events.

Nevertheless, the data is promising for a simplification of carotid risk stratification using CAS and provides strong evidence for conducting future studies that utilize a larger study sample to validate these initial findings. Findings from randomized clinical trials indicate that the benefit of CEA or stenting in this group of individuals is marginal. However, the further risk stratification offered by CAS has the potential to target subgroups that may benefit from intervention, although this must be confirmed in a randomized clinical trial. CAS may also provide a means to identify individuals who would benefit from more intensive clinical follow-up. While reliable multivariate analysis could not be conducted due to the limited sample size and event rate, CAS appeared to be more strongly associated with both plaque progression and new DLS than percent stenosis. This suggests that CAS may provide a better assessment on risk of stroke, beyond the current clinical angiographic solution, for asymptomatic patients with 50-79% stenosis.

Since maximum percent LRNC is the major input variable to CAS, the finding that CAS is positively associated with the incidence of new DLS ($p<0.001$) is consistent with the relationship between percent LRNC volume and DLS previously reported by Underhill, et al. (26) In the previous study, IPH was present in nearly 30% of the carotid arteries at baseline. In this study, it was shown that the risk associated with LRNC, as represented by CAS, holds in the subgroup without IPH at baseline.

While baseline CAS predicted incident DLS during follow-up, its relationship with new IPH was inconclusive. There were only four incidences of new IPH, and a positive association between CAS and new IPH was not found. However, all the new intraplaque hemorrhages occurred in subjects with CAS=2 and 3 at baseline. For subjects with CAS=4, 78% of them had IPH already at baseline. While a conclusion cannot be drawn from the small number of events seen here, this may suggest that IPH tends to occur at an earlier stage of plaque development and leads to growth into the higher levels of CAS, which is consistent with the concept of IPH as a primary driver of plaque growth, as shown previously. (25,27)

The MR plaque burden measure, mean NWI, appeared to predict new DLS or plaque progression well though not better than CAS. During the original development of CAS, mean NWI was not considered, though max NWI was as well as max WT and other plaque burden measures. In that cross-sectional analysis, max % LRNC area was more strongly associated with DLS and IPH than any plaque burden measures and thus CAS was based primarily on LRNC rather than plaque burden. From a biological perspective, it is expected that CAS, which is based on the presence and size of the LRNC, will provide a more precise measure of risk for plaque disruption than mean NWI, which is based solely on plaque size. For large plaques that are predominantly fibrotic or calcified, the risk for disruption predicted by mean NWI may vary from CAS. Future prospective studies may consider mean NWI as an additional predictor to confirm that this finding holds longitudinally.

S*tudy limitations:* The size of the study sample was not large and subjects were recruited from only two related centers. Furthermore, the rate of new events and the prevalence of CAS=4 in subjects without DLS or IPH were small, which also prevented reliable multivariate analysis to statistically compare the different potential predictors. Additionally, the association between the development of neurologic symptoms and CAS could not be

assessed due to the study design which required subjects to have completed both a baseline and 3 year follow up MRI of their plaques. Clinical guidelines at the recruitment centers indicate CEA for patients with 50-79% stenosis by US who become symptomatic and thus no follow up MRI was available in those cases. A larger, multi-center study is needed to have sufficient power to assess the ability of CAS for prediction of future ischemic events. Finally, 17% of patients were excluded in this study due to imaging issues. Recently developed 3-D MRI techniques such as 3D-MERGE and SNAP (29, 30) have been developed that will reduce the percentage of excluded subjects in future studies. Advantages of these new techniques include: 1) larger field of view and isotropic 3D scans which will improve co-registration of serially acquired scans and reduce the number of cases excluded due to insufficient coverage; 2) shorter scan time which may reduce exclusions due to motion artifact; 3) decreased artifact due to low-flow; and 4) higher contrast between IPH, surrounding vessel wall, and lumen.

Conclusions

CAS, based on two plaque parameters (maximum wall thickness and percent lipid-rich necrotic core), was found to have a significant increasing relationship with incident DLS and plaque progression in this prospective, longitudinal study of individuals with asymptomatic, 50-79% carotid stenosis. The CAS concept provides a method to further stratify risk beyond luminal stenosis and may allow more effective targeting of patients for specific treatment to prevent future stroke.

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Abbreviations

CAS	carotid atherosclerosis score
MRI	magnetic resonance imaging
DLS	disrupted luminal surface
FCR	fibrous cap rupture
IPH	intraplaque hemorrhage
WT	wall thickness
LRNC	lipid rich necrotic core
MRA	magnetic resonance angiography

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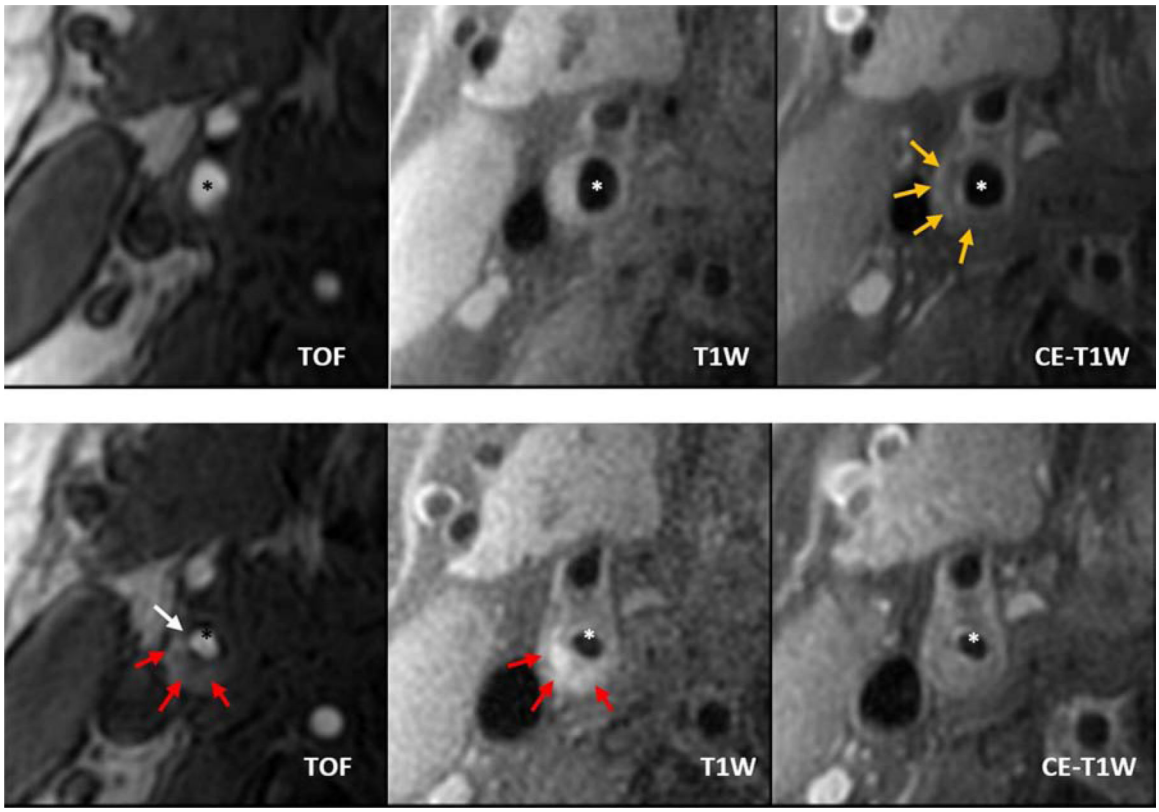

Figure 1. Baseline MRI (top row) demonstrating a CAS 4 internal carotid plaque with a large lipid rich necrotic core (yellow arrows)

The three-year follow-up MRI (bottom row) of the matched cross-section demonstrates fibrous cap rupture (white arrow) with intraplaque hemorrhage (red arrows). Also note the large increase in internal carotid wall area and decrease in lumen area. TOF = Time-of-Flight; T1W = pre-contrast T1-weighted image; CE-T1W = post-contrast enhanced T1-weighted image; * = lumen of the internal carotid artery.

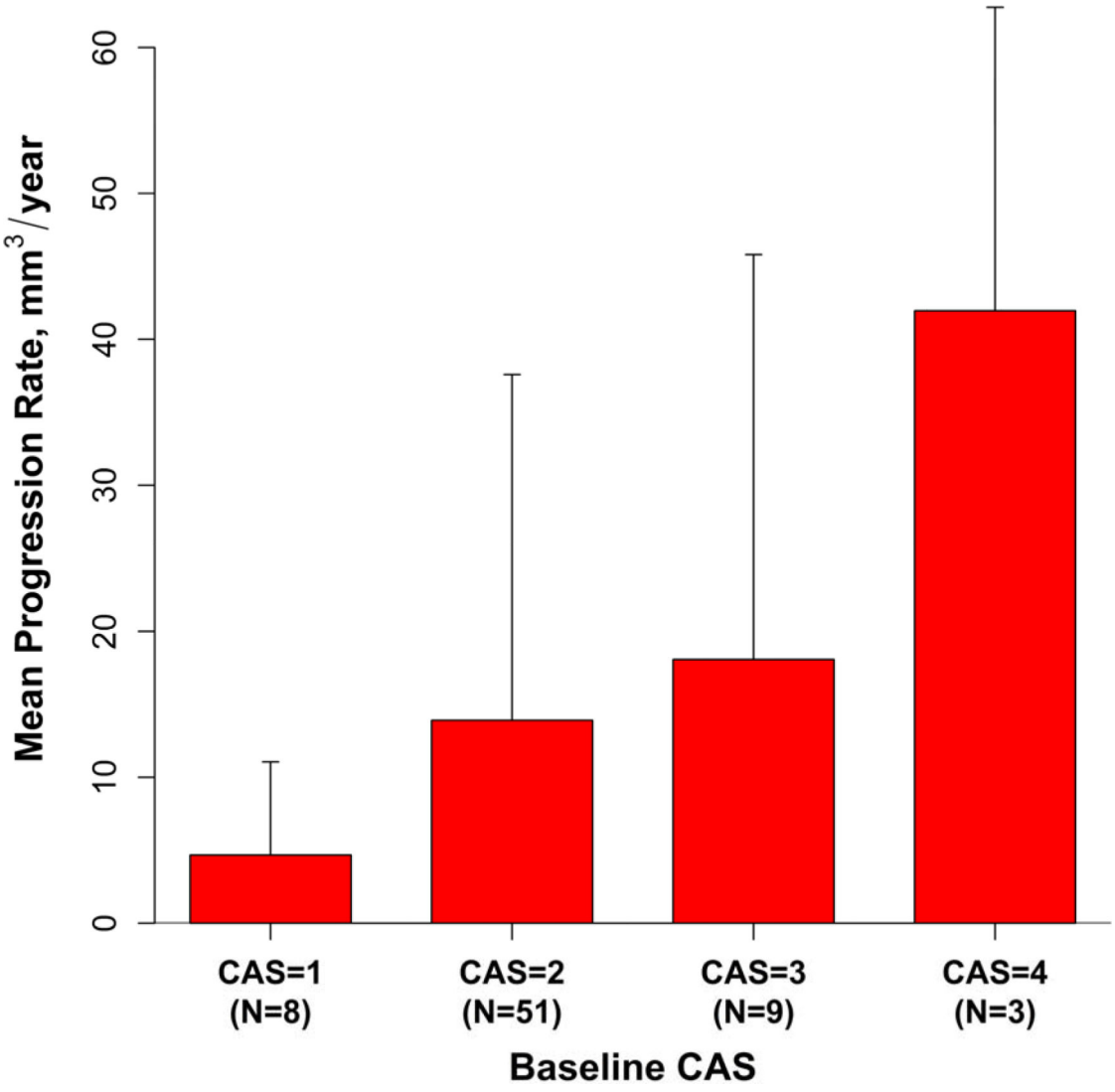

Figure 2. Mean annualized change in wall volume of subjects grouped by baseline CAS
The vertical bars represent 1 standard deviation.

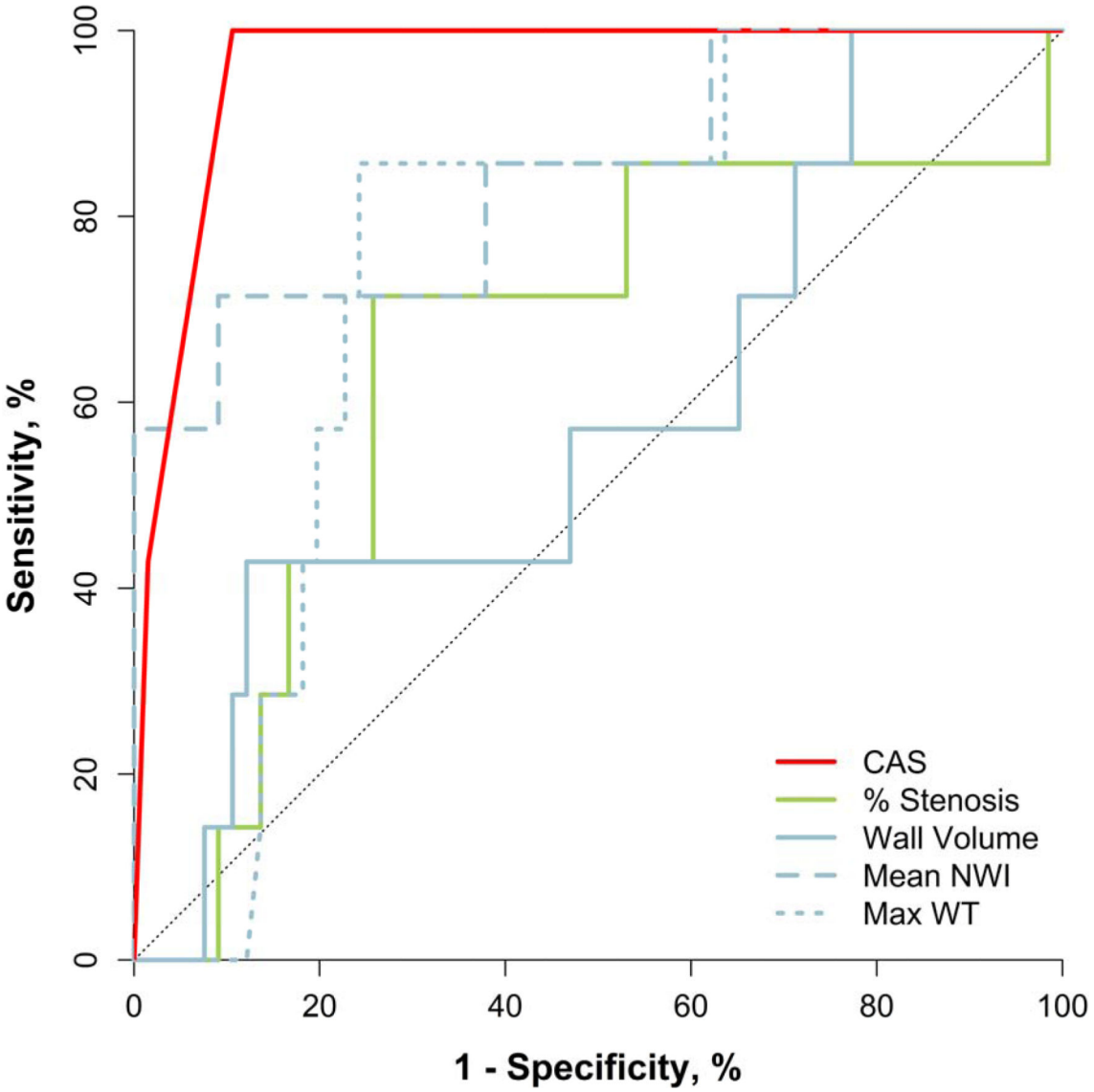

Figure 3. Receiver-Operator Characteristic (ROC) curves for individual predictors of new disrupted luminal surface (DLS)

CAS=carotid atherosclerosis score, NWI=normalized wall index, WT=wall thickness.

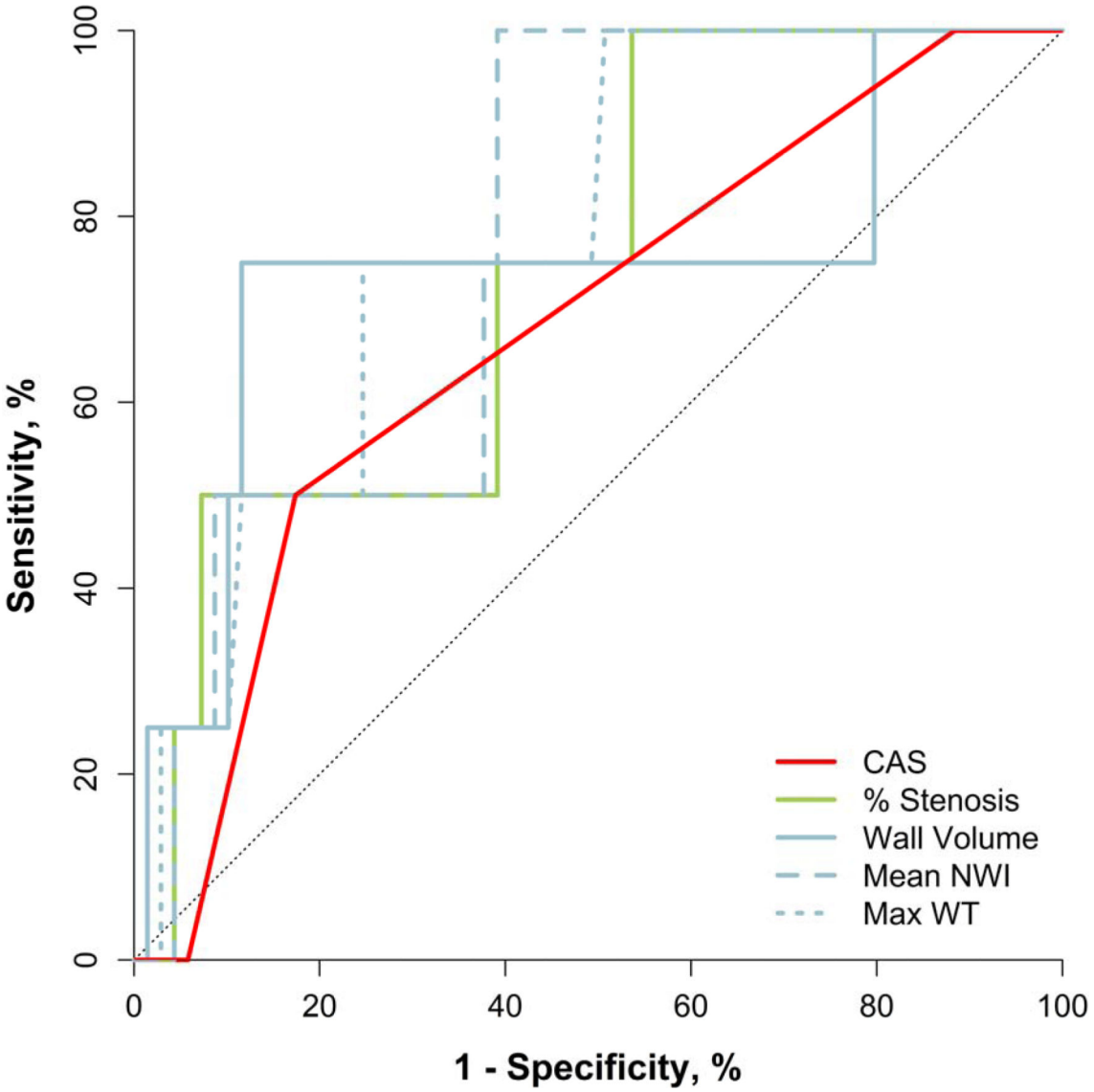

Figure 4. ROC curves for individual predictors of new IPH

CAS=carotid atherosclerosis score, NWI=normalized wall index, WT=wall thickness.

Table 1

Multi-contrast MRI Imaging Parameters

Sequence	T1w	T2w	PDw	TOF
Readout pulse	2D FSE	2D FSE	2D FSE	3D spoiled GRE
TR(ms)	800	2770	2770	23
TE(ms)	10	40	20	3.8
FOV	16 × 16	16 × 16	16 × 16	16 × 16
Matrix	256 × 256	256 × 256	256 × 256	256 × 256
Slice Thickness(mm)	2.0	2.0	2.0	2.0
NEX	2	2	2	2
No. of slices	12	12	12	24
Blood suppression	DIR	Mulitslice DIR	Mulitslice DIR	Venous in-flow saturation
Slice gap (mm)	0	0	0	−1.0
Flip angle	90	90	90	35
Scan time (min)	8	4	4	4

Table 2

Summary of patient demographics and baseline plaque burden at baseline (N=73).

Variable	Mean ± SD or N (%)	Range
Age, years	70.3 ± 9.6	45 – 89
Body mass index, kg/m^2 *	27.7 ± 5.4	18.9 – 54.3
Systolic blood pressure, mmHg *	144 ± 21	99 – 194
Male sex	62 (85)	-
Smoking status *	-	-
Never smoked	10 (14)	-
Quit	37 (51)	-
Active	25 (35)	-
Diabetes mellitus *	19 (26)	-
History of coronary artery disease *	31 (46)	-
History of hypertension	62 (85)	-
History of hypercholesterolemia	61 (84)	-
Statin therapy	51 (70)	-
Carotid stenosis, % †	29 ± 21	0 – 77
Wall volume, mm^3	660 ± 228	249 – 1327
Mean normalized wall index	0.52 ± 8	0.36 – 0.74
Max wall thickness	3.4 ± 1.2	1.3 – 7.7

* Excluding subjects missing measurement: 7 for body mass index, 1 for smoking status, and 5 for history of coronary artery disease.

† Measured from 3D TOF MRA using NASCET criteria.

Table 3

Incidence of new disrupted luminal surface (DLS) or intraplaque hemorrhage (IPH) by baseline CAS (N=73 subjects without DLS or IPH at baseline).

		N (%†)		
Baseline CAS	**N (%*)**	**DLS**	**IPH**	**DLS or IPH**
1	8 (11)	0 (0)	0 (0)	0 (0)
2	51 (70)	0 (0)	2 (4)	2 (4)
3	10 (14)	4 (40)	2 (20)	4 (40)
4	4 (5)	3 (75)	0 (0)	3 (75)
All	73 (100)	7 (10)	4 (5)	9 (12)
p for trend test		< 0.001	0.264	< 0.001

*Percent of total (N=73).

†Percent of subjects counted in each row (see second column).

Table 4

Predicting new disrupted luminal surface (DLS) or intraplaque hemorrhage (IPH) using a single baseline predictor: CAS, stenosis or a plaque burden measure (N=73 subjects without DLS or IPH at baseline).

	Outcome					
	DLS		IPH		DLS or IPH	
	AUC (95% CI)	p*	AUC (95% CI)	p*	AUC (95% CI)	p*
CAS	0.96 (0.92, 1.00)	<0.001	0.68 (0.42, 0.94)	0.142	0.86 (0.71, 1.00)	<0.001
Stenosis	0.65 (0.43, 0.88)	0.183	0.74 (0.52, 096)	0.110	0.69 (0.50, 0.89)	0.063
Wall volume	0.58 (0.36, 0.81)	0.465	0.74 (0.43, 1.00)	0.104	0.59 (0.37, 0.81)	0.383
Mean NWI	0.84 (0.67, 1.00)	0.003	0.78 (0.60, 0.95)	0.065	0.84 (0.70, 0.99)	0.001
Max WT	0.75 (0.60, 0.90)	0.030	0.78 (0.59, 0.97)	0.062	0.76 (0.62, 0.90)	0.013

AUC=area under the receiver operating characteristic curve, CI=confidence interval, NWI=normalized wall index, WT=wall thickness.

P-values were computed using an exact method, so are more reliable than the confidence intervals, which were computed using an approximation.

*Test for AUC > 0.5.

Table 5

Univariate correlations between plaque progression over three years and baseline CAS, stenosis and plaque burden (N=71 subjects who did not develop ulceration over follow up).

	r (95% CI)	p
CAS	0.26 (0.03, 0.47)	0026
Stenosis	−0.06 (−0.29, 0.18)	0.641
Wall volume	0.22 (−0.02, 0.43)	0.069
Mean NWI	0.23 (−0.01, 0.44)	0.057
Max WT	0.22 (−0.01, 0.43)	0.060

r = Pearson correlation coefficient, CI=confidence interval, NWI=normalized wall index, WT=wall thickness.