

# Asymptomatic carotid artery stenosis: a summary of current state of evidence for revascularization and emerging high-risk features

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## ABSTRACT

Carotid artery stenosis is a leading cause of ischemic stroke. While management of symptomatic carotid stenosis is well established, the optimal approach in asymptomatic carotid artery stenosis (aCAS) remains controversial. The rapid evolution of medical therapies within the time frame of existing landmark aCAS surgical revascularization trials has rendered their findings outdated. In this review, we sought to summarize the controversies in the management of aCAS by providing the most up-to-date medical and surgical evidence. Subsequently, we compile the evidence surrounding high-risk clinical and imaging features that might identify higher-risk lesions. With this, we aim to provide a practical framework for a precision medicine approach to the management of aCAS.

## INTRODUCTION

Asymptomatic carotid artery stenosis (aCAS) is defined as stenosis of extracranial carotid arteries without a history of ipsilateral ischemic stroke or transient ischemic attack. The estimated prevalence of severe aCAS ( $\geq 70\%$ ) increases with age and ranges from 0.1% to 3.1%,<sup>1</sup> with a population-attributable stroke risk of 0.7%.<sup>2</sup> Given its low prevalence and stroke risk, the United States Preventive Services Task Force currently recommends against screening for aCAS in the general adult population.<sup>3</sup> Nevertheless, 90% of carotid revascularizations in the United States are performed on patients with aCAS.<sup>4,5</sup>

The latest 2014 American Heart Association (AHA) guidelines for aCAS recommend consideration of carotid endarterectomy (CEA) in  $\geq 70\%$  stenoses, yet highlight the efficacy against modern medical treatment is 'not well established'.<sup>6</sup> Globally, heterogeneity in the 28 different national guideline recommendations abound.<sup>7</sup> This uncertainty stems from concurrent advancement of best medical therapy (BMT) and revascularization techniques after the conclusion of the now outdated aCAS level 1 evidence. Thus, understanding the available evidence on treatment strategies and identification of high risk features has gained importance.

## METHOD/SEARCH STRATEGY

We searched the electronic databases PubMed, Google Scholar, and EMBASE using the terms: stroke, asymptomatic carotid artery stenosis or artery, carotid ultrasound, transcranial Doppler, microembolic detection, carotid MRI, carotid plaque imaging, and/or silent brain infarction. We included original retrospective and prospective research studies including  $>100$  patients, systematic reviews, and meta-analyses.

## CURRENT EVIDENCE: SURGICAL INTERVENTION

### Carotid endarterectomy

Two landmark randomized controlled trials (RCTs—ACAS, ACST-1) compared CEA plus BMT with BMT alone in patients with aCAS ( $\geq 60\%$  stenoses) (table 1). ACAS found a 5-year risk of ipsilateral stroke, perioperative stroke, or death of 5.1% vs 11.0% in the CEA vs BMT arm ( $p < 0.004$ ).<sup>8</sup> ACST-1 found a 5-year risk of stroke and perioperative events of 6.4% vs 11.8% in the CEA vs BMT arm ( $p < 0.0001$ ).<sup>9</sup> As such, the 2011 AHA guidelines along with 13 other societal guidelines recommended CEA in patients with aCAS with  $\geq 70\%$  stenoses if perioperative stroke, myocardial infarction, and death rates were low.<sup>10</sup>

Soon after these trials were concluding, BMT had a dramatic overhaul with new stringent data-driven guideline recommendations, further detailed below. A 10-year follow-up of the ACST-1 trial demonstrated a decline in the stroke risk of the medical arm between the first and second 5-year periods, with the number needed to treat for CEA from 19 up to 22 as the proportion of patients receiving anti-hypertensives and lipid-lowering therapy rose from 53% and 10% to 88% and 81%, respectively.<sup>11</sup> Thus, controversy began regarding how modern BMT compared with CEA, with ongoing trials such as Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study (CREST-2) re-examining this question.<sup>12</sup>

### Carotid artery stenting (CAS)

Once CEA was established as the benchmark revascularization in aCAS, CAS was introduced and direct head-to-head comparison studies were undertaken. These include SAPHIRE (Stenting and Angioplasty with Protection in Patients at High

**Table 1** Landmark randomized controlled trials for carotid endarterectomy, carotid artery stenosis, transcatheter carotid artery revascularization, and their outcomes

Carotid endarterectomy						
	Recruitment period	No of patients	Population	Perioperative risk of any stroke and death	Risk of any stroke (including perioperative) and death	Number needed to treat*
ACAS <sup>8</sup>	1987–1993	1662	Asymptomatic (never symptomatic)	2.3%	5 year: 5.1% (CEA) vs 11.0% (BMT)	17
ACST-1 <sup>9</sup>	1993–2003	3120	Asymptomatic (6 months or longer)	3.1%	5 year: 6.4% (CEA) vs 11.8% (BMT)	19
Carotid artery stenting						Relative risk
SAPPHIRE <sup>13</sup>	2000–2002	334	Symptomatic (97)/asymptomatic (237)	5.5% (CAS) vs 8.4% (CEA), p=0.36‡	3 year: 21.4% (CAS) vs 29.2% (CEA)†	0.74 (95% CI 0.47 to 1.14)
CREST-1 <sup>14</sup>	2005–2008	2502	Symptomatic (1321)/asymptomatic (1181)	2.5% (CAS) vs 1.4% (CEA), p=0.15	10 year: 11.8% (CAS) vs 9.9% (CEA)†	1.10 (95% CI 0.83 to 1.44)
ACT-I <sup>15</sup>	2005–2013	1453	Asymptomatic	2.9% (CAS) vs 1.7% (CEA), p=0.33	5 year: 3.8% (CAS) vs 3.3% (CEA)†	1.14 (95% CI 0.61 to 2.15)
ACST-2 <sup>16</sup>	2008–2020	3625	Asymptomatic	3.7% (CAS) vs 2.7% (CEA), p=0.12	5 year: 5.3% (CAS) vs 4.5% (CEA)	1.11 (95% CI 0.91 to 1.32)
Transcatheter carotid artery revascularization						
ROADSTER-1 <sup>19</sup>	2012–2014	141	Symptomatic (36)/asymptomatic (105)	2.8%‡	No follow-up data	
ROADSTER-2 <sup>20</sup> §	2015–2019	692	Symptomatic (180)/asymptomatic (512)	1.4%	No follow-up data	

All reported risks specifically pertain to asymptomatic patients except for the SAPPHIRE and ROADSTER-1 trials that report combined risk of asymptomatic and symptomatic populations.

\*Number needed to treat to prevent one stroke.

†These trials include the incidence of myocardial infarction in addition to risk of any stroke and death.

‡The value represents numerical risk combined for both asymptomatic and symptomatic populations.

§Interim result of ongoing trial.

BMT, best medical therapy; CAS, carotid artery stenosis; CEA, carotid endarterectomy.

Risk for Endarterectomy), CREST (Carotid Revascularization Endarterectomy vs Stenting Trial), ACT-I (Randomized Trial of Stent vs Surgery for Asymptomatic Carotid Stenosis), and ACST-2 (Second Asymptomatic Carotid Surgery Trial).<sup>13–16</sup> A pooled analysis inclusive of three RCTs (SAPPHIRE, CREST-1, ACT-I) found that a composite outcome of any periprocedural stroke, death, or myocardial infarction (MI), or long-term ipsilateral strokes, was similar between interventions (RR 0.92; 95%CI 0.70 to 1.21).<sup>17</sup> The most recently published ACST-2 results also demonstrated similar efficacy and safety. Kaplan-Meier estimates of 5-year non-procedural stroke were 2.5% for fatal or disabling stroke in both CAS and CEA groups, and 5.3% vs 4.5% for any stroke in the CAS and CEA groups, respectively (RR 1.16; 95% CI 0.86 to 1.57).<sup>16</sup> Overall, cumulative evidence demonstrated similar outcomes for both interventions.

Owing to the improvement in BMT after completion of initial CEA and some of the CAS trials, the SPACE-2 (Stent Protected Angioplasty in Asymptomatic Carotid Artery Stenosis vs Endarterectomy) trial was designed as a three-arm comparison between BMT, CEA, and CAS.<sup>18</sup> Unfortunately, SPACE-2 was halted after 513 patients (vs the planned 3550) owing to poor enrollment. The 1-year interim analysis revealed a non-statistically different 1-year incidence of ipsilateral stroke in 2.0% of CEA, 3.0% of CAS, and 0.9% of BMT.<sup>18</sup> As previously highlighted, clinical equipoise on the role for CAS and CEA in the context of modern BMT exists with ongoing trials recruiting.

### Transcatheter carotid artery revascularization

Transcatheter carotid artery revascularization (TCAR) has emerged as an alternative to traditional transfemoral and transradial CAS. By performing direct common carotid access with continuous flow

reversal, it aims to avoid embolization from the aortic arch. In 2015, TCAR made its debut with the ROADSTER (Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure) trial. Seventy-five percent of its population were patients with aCAS. The single uncontrolled study demonstrated a stroke rate of 1.4% and composite stroke, death, and MI rate of 3.5%.<sup>19</sup> The follow-up ROADSTER-2 trial was designed to reflect the practice of multispecialty operators, with 81.2% of surgeons being TCAR naïve, although they were required to demonstrate proficiency with traditional CAS and undergo TCAR training. In that study of 632 patients, the 30-day postoperative stroke rate was 1.9% and the composite rate of strokes, death and MI rate 3.2%.<sup>20</sup> With only two small single-arm, short-term follow-up trials of TCAR compared with the multiple large long-term follow-up studies of CAS and CEA, further research is needed to assess the role of TCAR in the management of aCAS.

### CURRENT EVIDENCE: BEST MEDICAL THERAPY

BMT has dramatically evolved in comparison with its loose definition from early aCAS trials and now encompasses different antiplatelet regimens, lipid-lowering agents, stringent glucose and blood pressure management, and lifestyle modifications (as summarized in table 2). These improvements have led to declining stroke risk in patients with aCAS treated with BMT and therefore limit the applicability of prior landmark intervention trials. For example, the 5-year ipsilateral stroke risks in the medical arm of the 1995 ACAS trial and the 2010 ACST-1 were 11% and 3.6%, respectively.<sup>8,9,21</sup> A systematic review of 11 studies with a total of 3724 patients with aCAS receiving BMT found a dramatic decline in annual ipsilateral stroke risk from

**Table 2** Medical therapy used in prior landmark randomized controlled trials vs contemporary best medical therapy

Definition of medical treatment in prior RCTs		Modern BMT
1980s	VACS <sup>73</sup>	Lipid-lowering <sup>74,75</sup> : atorvastatin 40–80 mg or rosuvastatin 20–40 mg (SPARCL)±ezetimibe with target LDL<70 mg/dL. Despite maximal statin and ezetimibe therapy and LDL>70 mg/dL, PCSK9 inhibitor can be used Blood pressure. <sup>75</sup> Target BP <130/80 mm Hg or <140/90 mm Hg (previously <140/90 mm Hg alone) Antiplatelet: 2018 <sup>76</sup> - POINT trial showed the reduction in recurrent ischemic events at 90 days when patients with minor stroke or high-risk TIA were treated with aspirin 50–325 mg and clopidogrel 75 mg followed by initial loading dose of aspirin 50–325 mg and clopidogrel 600 mg 2020 <sup>77</sup> -THALEz trial showed the reduction in recurrent ischemic events at 90 days when patients with a mild–moderate acute non-cardioembolic stroke or with a high-risk of a TIA were treated with aspirin 75–100 mg and ticagrelor 90 mg twice per day followed by initial loading dose of aspirin 300–325 mg and ticagrelor 180 mg Rest as per 2021 AHA guideline <sup>75</sup> : Diabetes mellitus: HbA1c ≤7 (multidimensional care: nutritional education, lifestyle counseling, medication) Smoking cessation: counseling with or without drug therapy (nicotine replacement, bupropion, or varenicline) Obesity: behavioral lifestyle-modification program Diet: Mediterranean diet Obstructive sleep apnea: Treatment with positive airway pressure
	Aspirin 650 mg twice/day or 325 mg/day unable to tolerate	
1990s	ACAS <sup>8</sup>	
	Aspirin 325 mg/day. 'Discussion' of hypertension, diabetes mellitus, abnormal lipid levels, excessive alcohol and tobacco use	
2000s	ACST-1 <sup>9</sup>	
	Antiplatelet, antihypertensive, lipid-lowering therapy. Lipid-lowering drugs: 10%→81%, BP therapy: 53%→88%, notable increase between 1993 and 2007.	

[AHA, American Heart Association; BP, blood pressure; LDL, low-density lipoprotein; TIA, transient ischemic attack.]

2.8% to 1.4% between 1985 and 2007. This correlated with a 32% increased prevalence of high total cholesterol diagnosis, a 22% increase in antiplatelet use, and a 14% decrease in current smoking status.<sup>22</sup>

Evidence suggests that the rate of stroke with BMT is quickly approximating 1%/year.<sup>22–24</sup> In parallel, CAS and CEA have become safer, with declining perioperative risk approaching 1%.<sup>25</sup> Limitations of BMT include its dependency on compliance for durability, which is the subject of much research. In fact, even in the ongoing CREST-2 study, adherence to hypertension guideline-based regimens is only 34%.<sup>26</sup> Overall, the optimal management of aCAS remains unclear. While we await the conclusion of CREST-2, it seems most logical to select patients with aCAS who are deemed to have a higher risk of developing stroke despite receiving fully optimized BMT.

### CLINICAL RISK ASSESSMENT

Clinical features of patients with aCAS may play a role in determining the risk of future ischemic events and assist in treatment decisions. The Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study remains as the largest prospective clinoradiographic correlation study of 1121 patients with aCAS treated with BMT.<sup>27</sup> Factors associated with higher stroke risk included age by 10-year increase (HR 1.42; 95% CI 1.00 to 2.02), increased serum creatinine by 20% increase (HR 1.28; 95% CI 1.09 to 1.50), history of contralateral ischemia (HR 3.03; 95% CI 1.77 to 5.20), systolic blood pressure by 10 unit increase (HR 1.11; 95% CI 1.07 to 1.22), and history of 10 or more smoking pack-years (HR 1.65; 95% CI 1.16 to 2.34).<sup>27</sup>

Although ACSRS demonstrated a higher risk of stroke in the presence of contralateral ischemic events, surgical revascularization in patients with severe contralateral carotid artery stenosis or occlusion has limited efficacy.<sup>28–30</sup> In fact, in the ACAS trial, patients with contralateral occlusions fared worse, with a 5-year ischemic event rate of 3.5% and 5.5% in the BMT and CEA arms, respectively.<sup>28</sup>

### EMERGING IMAGING RISK FACTORS

Imaging characteristics that can predict higher risk of ischemic stroke have emerged and hold promise in patient selection in the absence of conclusive universal evidence. A recent meta-analysis of 64 studies and 20 751 patients with carotid stenosis found a 26.5% incidence of high-risk features with a correlative increase in the rate of ipsilateral ischemic stroke (4.3 vs 1.2 events per 100 person-years; OR 3.0; 95% CI 2.1 to 4.3).<sup>31</sup> These features are means to uncover the risk for development of the two main pathophysiological causes of stroke in carotid stenosis, hypoperfusion and thromboembolism. Hypoperfusion results from increasing stenosis and a failure of collaterals.<sup>32</sup> Thromboembolism results from exposure of highly thrombogenic necrotic plaque core material following plaque rupture.<sup>33,34</sup> Imaging features that can identify steps in the progression towards plaque rupture or rupture itself are of especial interest. In the continuum of plaque evolution, expansion over time leads to the formation of a lipid-rich necrotic core, neovascularization, and intraplaque hemorrhage (IPH), which then can result in thinning of the atheroma's fibrous cap and ultimately rupture (table 3).<sup>35</sup>

### Transcranial Doppler Microembolic detection

Transcranial Doppler (TCD) high-intensity transient signals (HITS) represent a microembolic phenomenon.<sup>36</sup> TCD-HITS has been performed for decades with well-established methodology, and successful insonation can be achieved in about 90% of patients (figure 1A).<sup>37</sup> Its predictive value for future strokes in patients with aCAS has been well-validated in several studies, of which the largest and most recent is the ACES (the Asymptomatic Carotid Emboli Study). In this multicenter prospective observational study involving 467 patients with aCAS (≥60% stenosis), the incidence of at least one HITS was 16.5%, which was associated with a sixfold increased risk of ipsilateral stroke (HR 5.90, p<0.006) during the 2-year follow-up period.<sup>38</sup> Furthermore, a concurrent meta-analysis including five other observational studies (n=1144 patients) showed an almost sevenfold increase in ipsilateral stroke risk (OR 6.63, p=0.001).<sup>38</sup>

**Table 3** Summary of high-risk features in patients with asymptomatic carotid artery stenosis

Microembolic detection <sup>38*</sup>			
Study	Ipsilateral strokes with embolic signals	Without embolic signals	OR (95% CI)
ACES <sup>38</sup>	5/77 (6.5%)	5/390 (1.3%)	5.35 (1.51 to 18.94)
Abbott <i>et al</i> <sup>78</sup>	2/60 (3.3%)	4/171 (2.3%)	1.44 (0.26 to 8.07)
Molloy and Markus <sup>79</sup>	1/12 (8.3%)	0/30 (0%)	7.96 (0.30 to 209.7)
Orlandi <i>et al</i> <sup>80</sup>	3/6 (50.0%)	0/15 (0%)	31.00 (1.29 to 747.03)
Slebler <i>et al</i> <sup>81</sup>	1/8 (12.5%)	1/56 (1.8%)	7.86 (0.44 to 140.14)
Spence <i>et al</i> <sup>82</sup>	5/32 (15.6%)	3/287 (1.0%)	17.53 (3.97 to 77.38)
Total	17/195 (8.7%)	13/949 (1.4)	6.63 (2.85 to 15.44)
Plaque echolucency <sup>43*</sup>			
Study	Ipsilateral strokes with echolucent plaque	With echogenic plaque	RR (95% CI)
Grønholdt <i>et al</i> <sup>83</sup>	8/63 (12.7%)	7/48 (14.6%)	0.87 (0.34 to 2.23)
Mathiesen <i>et al</i> <sup>84</sup>	5/100 (5.0%)	1/77 (1.3%)	3.85 (0.46 to 32.28)
Nicolaides <i>et al</i> <sup>85</sup>	28/409 (6.8%)	21/677 (3.1%)	2.23 (1.28 to 3.87)
O'Holleran <i>et al</i> <sup>86</sup>	13/88 (14.8%)	6/205 (2.9%)	5.12 (2.01 to 13.04)
Polak <i>et al</i> <sup>87</sup>	30/856 (3.5%)	73/4030 (1.8%)	1.96 (1.25 to 2.90)
Silvestrini <i>et al</i> <sup>88</sup>	8/61 (13.1%)	31/560 (5.5%)	2.58 (1.13 to 5.89)
Topakian <i>et al</i> <sup>89</sup>	8/164 (4.9%)	2/271 (0.7%)	6.61 (1.42 to 30.75)
Total	100/1741 (5.7%)	141/5868 (2.4%)	2.48 (1.90 to 3.22)
Progression of stenosis			
Study	Ipsilateral strokes with progression	Without progression	RR (95% CI)
Conrad <i>et al</i> <sup>65*</sup>	36/262 (13.7%)	54/638 (8.5%)	1.62 (1.09 to 2.41)
Kakkos <i>et al</i> <sup>57</sup>	19/222 (8.6%)	40/899 (4.5%)	1.92 (1.14 to 3.25)
Total†	55/484 (11.4%)	94/1537 (6.1%)	1.86 (1.35 to 2.55)
Reduced cerebrovascular reserve (CVR)			
Study	Ipsilateral strokes in normal CVR	Impaired CVR	OR (95% CI)
Gur <i>et al</i> <sup>90</sup>	0/23 (0.0%)	2/21 (9.5%)	6.03 (0.27 to 133.11)
Silvestrini <i>et al</i> <sup>43</sup>	4/54 (7.4%)	8/40 (20.0%)	3.13 (0.87 to 11.24)
Kimiagar <i>et al</i> <sup>91</sup>	0/14 (0.0%)	6/21 (28.6%)	12.16 (0.63 to 235.70)
Total‡	4/91 (4.4%)	16/82 (19.5%)	5.27 (1.68 to 16.51)
Intraplaque hemorrhage (IPH)			
Study	Ipsilateral strokes with IPH	Without IPH	HR (95% CI)
Schindler <i>et al</i> <sup>70</sup>	8/40 (20.0%)	2/96 (2.1%)	14.5 (2.9 to 7.25)
Ipsilateral silent brain infarction (SBI)			
Study	Annual stroke rate with prior ipsilateral SBI	Without prior ipsilateral SBI	HR (95% CI)
Kakkos <i>et al</i> <sup>54</sup>	3.6%	1.0%	3.0 (1.46 to 6.29)

\*This study used ipsilateral neurologic symptom as outcome measure, including ipsilateral stroke, transient ischemic attack, or amaurosis fugax rather than solely ipsilateral strokes.

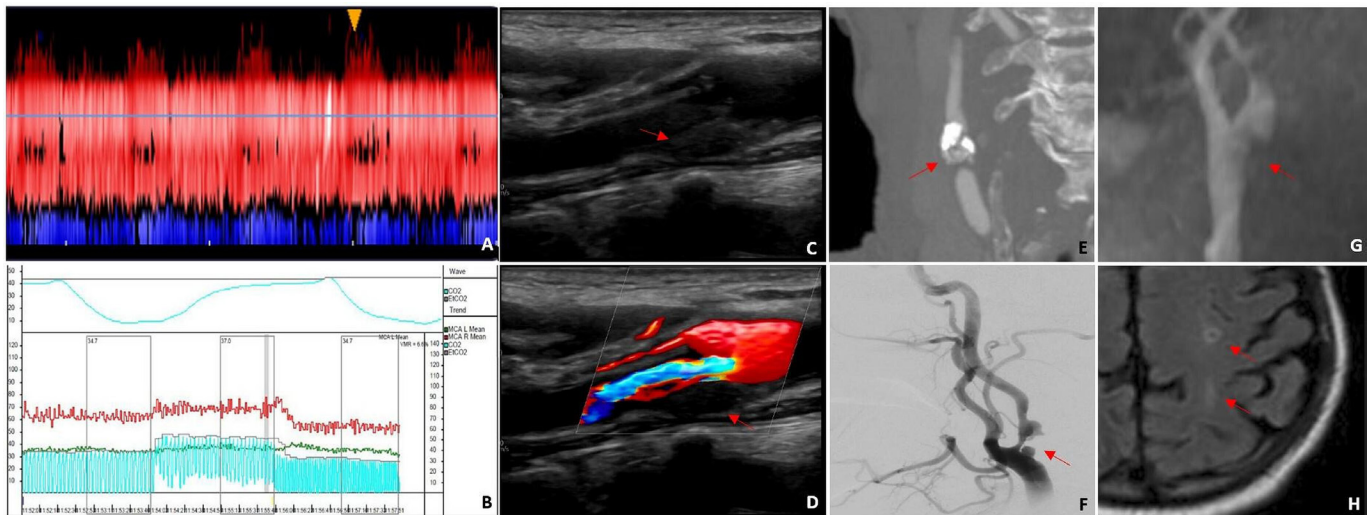
†Calculation derived from authors.

‡The list of studies obtained these meta-analyses.<sup>38, 43</sup>

TCD-HITS has also been used as a potential measure of treatment efficacy. A prospective study including 468 patients with ≥60% asymptomatic carotid stenosis observed a reduction in the prevalence of HITS from 12.6% in patients recruited prior to 2003 versus 3.7% between 2003 and 2007, with the latter group taking significantly more statins, antihypertensives, and antiplatelet therapy.<sup>39</sup> Post-CEA studies also demonstrated near-complete disappearance of HITS in the following days after CEA.<sup>40, 41</sup> Limitations of this technology are its 10% failure rate of ensonation and operator dependency; however, robotic TCD technology holds promise in removing operator dependency.<sup>42</sup> Overall, TCD is cost-effective, radiation-free, and widely available, with significant predictive value.

### Cerebrovascular reactivity

Cerebrovascular reactivity (CVR) measures the vascular reserve downstream of a stenotic vessel. Circulations under chronic hypoperfusion will compensate by dilating downstream vasculature to increase blood flow to normal levels. As such, a chronically compensated circulation is maximally dilated and will not respond to further vasodilatory stimuli, by extension it is a circulation at risk of hypoperfusion infarcts from carotid stenosis. One of the most commonly used technique to assess for CVR uses TCD; this involves monitoring middle cerebral artery mean flow velocities (MFVs) before and after a vasodilatory challenge, such as breath-holding or CO<sub>2</sub> inhalation.



**Figure 1** High-risk imaging features. (A) Transcranial Doppler (TCD) with high-intensity transient signal (HITS) marked by yellow arrow. (B) TCD cerebrovascular reactivity (TCD-CVR) in a patient with impaired vascular reserve on the left (green line) after CO<sub>2</sub> inhalation. (C) B-mode and corresponding (D) color Doppler of an echolucent plaque (red arrow) on carotid ultrasound. Ulcerated plaques (red arrows) on (E) CT angiography, (F) digital subtraction angiography and (G) MR angiography. (H) Silent brain infarction on MRI-T2W images (red arrows).

Patients with poor CVR will have similar TCD velocities before and after vasodilatory challenge compared with normal CVR, in which velocities increase after challenge (figure 1B). Breath-holding studies report a breath-holding index (BHI):

$$\frac{(\text{MFV}(\text{bh}) - \text{MFV}(\text{base})) / \text{MFV}(\text{base})}{\text{time (seconds)}}$$

where MFV(bh) is mean flow velocity during breath holding and MFV (base) is MFV at baseline. A BHI of <0.69 is considered poor.<sup>43</sup> If CO<sub>2</sub> inhalation technique is used, the CVR calculation is the same as the above formula except the change in MFV is divided by the rise in PCO<sub>2</sub>. Poor CVR is defined as a rise in MFV <2.0% mm Hg PCO<sub>2</sub>.<sup>44</sup>

In a meta-analysis (13 studies; 991 patients) including both patients with asymptomatic and symptomatic carotid stenosis, CVR impairment was associated with a fourfold increased stroke risk (OR 3.96; 95% CI 2.60 to 6.04).<sup>45</sup> Of these 13 studies, three studies including 152 patients were strictly performed in the aCAS population with a similar fourfold increased stroke risk (OR 4.00; 95% CI 1.27 to 12.60). Limitations include heterogeneous definition of poor CVR and its capacity to screen only for less prevalent low perfusion type ischemia.

## Carotid ultrasound

### Plaque echolucency

Plaques with lipid-rich necrotic cores or IPH appear echolucent on carotid ultrasound (figure 1C,D).<sup>46</sup> Although qualitative assessments can be used, the lack of standardization in image acquisition makes normalization important. Some quantitative methods exist, like the Gray-Weale and the Gray-Scale median, which provide such standards.<sup>47</sup> A meta-analysis of seven studies with 7557 patients with aCAS and mean follow-up of 3 years, found an increased risk of ipsilateral stroke across all stenosis severities in subjects with echolucent plaques compared with echogenic (RR 2.31; 95% CI 1.58 to 3.39; *p*<0.001).<sup>48</sup> These findings were reproduced in a post hoc analysis of the ACST-1 trial medical arm, demonstrating higher 5-year ipsilateral stroke risk in patients with echolucent plaque (HR 2.52; 95% CI 1.20 to 5.25; *p*=0.014).<sup>49</sup> In ACES, the combination of plaque echolucency and TCD-HITS was associated with a more than 10-fold increased risk of ischemic stroke (HR 10.61; 95% CI 2.98 to 37.82).<sup>38</sup>

The distribution of the echolucency within the plaque can also assist prediction. A juxtaluminal location has been found to be of higher risk than a central location.<sup>50</sup> This led to the derivation of the juxtaluminal black area (JBA), representing fresh thrombotic components on the plaque surface without an overlying fibrous cap.<sup>51</sup> Histopathologically, this correlates with thinned/ruptured cap, intraplaque hemorrhage, surface thrombus, and cap inflammation.<sup>52</sup> Computer-assisted quantification has shown that a JBA ≥8 mm<sup>2</sup> is an independent predictor of ischemic events. The ACSRS study had similar results, with an annual stroke rate found to be 0.4% vs 3.2% in JBA <4 and >8 mm<sup>2</sup>, respectively.<sup>53</sup> Heterogeneity in reporting and inter-reader variability are shortcomings of this feature, yet it can be easy to incorporate in practice given its wide availability and low cost.

### Progression of stenosis

Severity of carotid stenosis has long been linked with stroke risk and is frequently used to make treatment decisions. The ACSRS study showed a parallel increase in annual stroke risk over increasing severity of stenosis (50–69%, 0.8%; 70–89%, 1.4%; 90–99%, 2.4%).<sup>54</sup> Moreover, progression of stenosis over time is frequently monitored to make treatment decisions, and data suggest that it can be associated with stroke risk. The incidence of progression of stenosis in asymptomatic carotid stenosis ranges between 9.0% and 29.1%.<sup>55–57</sup> The ACSRS study demonstrated the 8-year cumulative ipsilateral stroke rate to be 0% in patients who had regression of stenosis, 9% in unchanged, and 16% in progression of stenosis (RR 1.92; 95% CI 1.14 to 3.25).<sup>57</sup> In that study, stenoses were graded into six classes, 50–59%, 60–69%, 70–79%, 80–89%, 90–95%, and 96–99%. Progression was defined as a change to at least one class up. Another study focusing on moderate asymptomatic stenosis (50–69%), with median follow-up of 3.6 years, showed similar results of 8.5% vs 13.7% ipsilateral ischemic events in non-progressors versus progressors, respectively (RR 1.62; 95% CI 1.09 to 2.41).<sup>55</sup> Also, progression was found in 29.1% of patients despite >85% use of antiplatelet and lipid-lowering agents. While progression of stenosis is almost universally monitored, its usefulness in prediction is frequently overlooked. This can be monitored through many different modalities, including

ultrasound, CT angiography (CTA) or MR angiography (MRA); the last of these with the most limited resolution.

### Plaque ulceration

Plaque rupture has been defined as an intimal defect larger than 1 mm in width, signifying a prior plaque rupture and exposing the necrotic core that serves as potential source of thromboembolic events.<sup>58–59</sup> The prevalence of plaque ulceration in asymptomatic carotid artery stenosis is shown to be 13.1%.<sup>31</sup> While diagnostic cerebral angiography is considered as a gold standard, CTA and MRA have demonstrated comparable sensitivity and specificity of >90% (figure 1E–G).<sup>60–61</sup> On the other hand, carotid ultrasound has far inferior sensitivity, of the order of 30%.<sup>62–63</sup> In one study using 3D ultrasound, the detection of more than one ulceration in patients with aCAS was associated with an increased risk of ipsilateral ischemic strokes in 3 years (no ulcer vs ulcer, 1.4% vs 7.1%,  $p < 0.049$ ).<sup>64</sup> A limitation is the scarcity of studies using plaque ulceration as a predictor for future ipsilateral ischemic events in patients with aCAS, and hence needs further validation. However, its usefulness should not be underestimated as plaque ulceration has been strongly associated with a significantly higher rate of ipsilateral stroke in patients with symptomatic CAS in high-quality studies.<sup>59–65</sup>

### Magnetic resonance imaging

#### Intraplaque hemorrhage

IPH is a major driver of plaque progression and rupture. Several clinical and research-based MRI techniques can detect IPH, including T1-weighted imaging, fat-suppressed 2D or 3D, magnetization-prepared rapid acquisition gradient-echo imaging, and time-of-flight MRA imaging.<sup>66–68</sup> The more widely available clinical T1-weighted images can detect IPH with sensitivity and specificity of 80% and 97%, respectively.<sup>69</sup> A meta-analysis of seven studies using T1-weighted imaging found an IPH incidence of 29.4% in aCAS with a significant increased risk in ipsilateral stroke (no IPH vs IPH, 0.8 vs 5.4%/year, HR 7.9, 95%CI 1.3 to 47.6) during the 30-month follow-up period.<sup>70</sup> The limitations are higher costs with the need for specialized sequences and its tendency to overestimate the degree of non-severe carotid stenosis<sup>71</sup>; yet with rapidly evolving technologies, there is unquestionable potential.

#### Ipsilateral silent brain infarction

Silent brain infarctions (SBIs) are asymptomatic radiographic infarcts in the downstream territory of a stenotic carotid (figure 1H). The ACSRS found a prevalence of 18% ipsilateral SBI during mean follow-up of 44.6 months, with a threefold increased risk of future ipsilateral ischemic stroke (no SBI vs SBI, 1.0% vs 3.6%,  $p = 0.002$ ).<sup>54</sup> Although these lesions are asymptomatic owing to their small size and location, their accumulation can increase the risk of cognitive impairment and vascular dementia.<sup>72</sup> The limitation is the poor specificity and lack of consensus. However, SBI can be frequently obtained from initial imaging evaluations of patients with aCAS, making it an easily available predictor.

### CONCLUSION

Modern medical and surgical advances have continued to improve the outcomes of patients with carotid stenosis. Available decades-old level 1 evidence of aCAS treatment has become outdated and new ongoing trials, like CREST-2, are needed to uncover the optimal management. Mounting evidence suggests that imaging-based identification of high-risk features may aid

in selecting patients with higher risk aCAS who may maximally benefit from surgical revascularization. Taken together, until new evidence becomes available, it is reasonable to replace the ‘one-size-fits-all’ with a practical personalized medicine approach.

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