Asymptomatic Carotid Stenosis: Several Guidelines with Unclear Answers

Asymptomatic carotid stenosis (ACS) is commonly defined as the presence of atherosclerotic narrowing of the proximal internal carotid artery by ≥50% at the level of bifurcation in individuals with no history of recent (within the last six months) ischemic stroke/TIA involving ipsilateral carotid territory.[1] Although the presence of 50%–69% narrowing is considered as moderate stenosis, narrowing ≥70% is generally considered as severe stenosis.[2] However, there are no standard criteria proposed on the severity of stenosis and duration of recent ischemic event and definitions vary among studies depending on the method used for assessment of stenosis. Some criteria also use >60% definition. Table 1 summarises the definitions of all major trials addressing the management of ACS.

The importance of optimal management ACS comes from the fact that it is not just a risk factor for stroke but to coronary artery disease and mortality as well. Results from the Second Manifestations of ARTerial disease (SMART) study provides evidence that patients with ACS should be treated optimally as they are at risk of vascular events (HR 1.5; 95% CI 1.1–2.1) and mortality (HR 1.8; 95% CI 1.2–2.6).[8] However, the management of ACS remains controversial, largely because only a small proportion of patients are ever destined to suffer a stroke, along with growing evidence that the risk of stroke declines with modern medical therapy, risk factors control and statin use.

What Do the Guidelines Say?

A significant controversy in the management of patients with ACS is the selection of patients for carotid revascularisation, notably in the face of evidence that ipsilateral strokes on optimal medical therapy have declined significantly over time. Table 2 summarises all the available guidelines published till date addressing the management of ACS.[9] The evidence supporting these recommendations is largely drawn from the randomised controlled trials (RCTs) explained below. The 2017 European Society of Vascular Surgery guidelines (ESVS) suggest that carotid endarterectomy (CEA) (class IIa recommendation, level of evidence B) or carotid stenting (class IIb, level of evidence B) should be considered for patients with ACS (60%–99%) at average surgical risk, provided the documented perioperative stroke/death rate is less than 3% and the patient's life expectancy exceeds 5 years.[10] This is in line with the other guidelines.[11-14] Although all the guidelines suggest forming a multidisciplinary

Table 1: Definitions of asymptomatic carotid stenosis used in major studies

Study	Publication (year)	Mode of assessment	Severity of stenosis	Duration of last ipsilateral CORI
ACAS[3]	1995	Arteriogram	>60%	Not mentioned
		USG Doppler (for confirmation)		
ASCT-1[4]	2010	USG doppler	>60% (no fixed cut-off)	>180 days
CREST-1[5]	2010	Angiography	>60%	>180 days
		USG doppler	>70%	
		CTA/MRA	>80%	
ACT-1[6]	2016	Angiography or doppler USG or both	70-99%	>180 days
SPACE-2[7]	2016	USG	70-99% (ECST)	>180 days

CORI: Cerebrovascular or retinal ischemic event, CTA: Computed tomography angiography, MRA: Magnetic resonance angiography, USG: Ultrasonography

Table 2: Summary of recommendations on the management of asymptomatic carotid stenosis

Organisation	Publication (year)	Recommendations			
		CAS	"High risk for CEA" CAS	CEA	Multidisciplinary team
RACP[14]	2010	Should not be performed in majority of patients	NA	Gold standard	Determining suitability for procedures is often done as a team approach
SVS[12]	2011	Insufficient data	Should not be performed	I	No comment
AHA[13] ACCF[13]	2011	IIb	IIa	IIa	No comment
ESVS[10]	2017	IIb	IIb	IIa	I
ESC/ESVS[11]	2017	IIb	IIa	IIa	I

ACCF=American College of Cardiology Foundation; AHA=American Heart Association; CAS=Carotid artery stenting; CEA=Carotid endarterectomy; ESC=European Society of Cardiology; ESVS=European Society for Vascular surgery; RACP=Royal Australasian College of Physicians; SVS=Society for Vascular Surgery; Levels of recommendation: Class I (Strong): Benefit >>> risk. Intervention is recommended, Class IIa (Moderate): Benefit >> risk. Intervention is reasonable, Class IIb (Weak): Benefit ≥ risk. Intervention may be considered, Class III (Moderate or strong): Benefit ≤ risk. Intervention is not recommended or potentially harmful

Table 3: Randomised controlled trials comparing CEA vs medical treatment alone in patients with asymptomatic carotid stenosis

Trial (Year)	*n*	Follow-up	30-day stroke and death		Long-term stroke rate			*P*
			CEA	MT	Definition	CEA	MT	
VA cooperative group[15] (1993)	444	Mean 4.0 years	4.7%	1.3%	Ipsilateral TIA, transient monocular blindness, stroke	8.0%	20.6%	<0.001
ACAS[3] (1995)	1662	Median 2.7 years	2.3%	0.4%	Periprocedural stroke or death, and postoperative ipsilateral stroke	5.1%	11.0%	0.004
ACST-1[4] (2010)	3120	Median 6.1 years	2.6%	0.7%	Any stroke or perioperative death	5Y: 6.9%	10.9%	0.0001
						10Y: 13.4%	17.9%	0.009
SPACE-2[7] (2019)	316	Interim - 1 year	2.5%	NA	Any stroke or perioperative death	2.5%	0.9%	N.S.
AMTEC[28] (2015)	55	Median 3.3 years	NA	NA	Any non-fatal ipsilateral stroke and death	6.5%	37.5%	0.008

ACAS: Asymptomatic carotid atherosclerosis study, ACST-1: Asymptomatic carotid surgery trial 1, AMTEC: Aggressive medical treatment evaluation for asymptomatic carotid artery stenosis, CEA: Carotid endarterectomy, MT: Medical treatment, N.S: Not specified, NA: Not available

Table 4: Randomised controlled trials comparing CEA vs CAS in patients with asymptomatic carotid stenosis

Trial (Year)	*n*	Follow-up	30-day MI, stroke and death			Long-term stroke rate			*P*
			CEA	CAS	*P*	Definition	CEA	CAS	
SAPPHIRE (subgroup)[16] (2008)	237	78% at 3 years	10.2%	5.4%	0.2	Periprocedural MI, stroke, death and post-procedural ipsilateral stroke, death	29.2%	21.4%	N.R.
CREST-1 (subgroup)[5] (2010)	1181	Median 7.4 years	3.6%	3.5%	N.S.	Periprocedural MI, stroke, death and post-procedural ipsilateral stroke	5Y: 5.4%	6.1%	0.95
							10Y: 10.1%	9.6%	
ACT-1[6] (2016)	1453	Up to 5 years	2.6%	3.3%	0.60	Post-procedural ipsilateral stroke	2.7%	2.2%	0.51
SPACE-2[7] (2019)	400	1 year	2.5%	2.5%	N.S.	Any stroke or perioperative death	2.5%	3.0%	N.S.

ACT-1: Asymptomatic carotid trial 1, CAS=Carotid artery stenting, CEA=Carotid endarterectomy, CREST-1: Carotid revascularisation endarterectomy versus stenting trial, MI=Myocardial Infarction, N.R.= Not reported, N.S.= Not significant, SAPPHIRE: Stenting and angioplasty with protection in patients at high risk for endarterectomy

Table 5: Summary of optimal medical therapy[27]

Treatment	Details
Life style modification	Smoking cessation, moderation of alcohol intake, moderate intensity exercise 4 to 7 days per week, at least 150 min per week, Mediterranean diet
Antithrombotic therapy	Aspirin 75-325 mg/day
	Clopidogrel 75 mg per day
	Ticagrelor 90 mg BD (if intolerant or allergic to Aspirin)
Lipid-lowering therapy	LDL target <70 mg/dL
	High-dose statin
	If not controlled - add ezetimibe, PCSK9 inhibitor
Antihypertensive therapy	Target <130/80 mm Hg
Glucose-lowering therapy	Target HbA1c <7.0%

LDL=Low-density lipoprotein

team for the management of these patients, the recommendations are not clear when it comes to carotid artery stenting (CAS) in both patients at average risk and high risk of complications of CEA.

Carotid Revascularisation and the Evolution of Medical Management

The current evidence on management of ACS is based on several landmark trials. Three randomised controlled trials (RCTs) conducted in the 1990s investigated whether CEA could reduce the risk of stroke in patients with asymptomatic carotid stenosis, namely VA cooperative study group, Asymptomatic carotid atherosclerosis study (ACAS) and Asymptomatic carotid surgery trial 1 (ACST-1) trials.[3,4,15] [Table 3] These trials predominantly recruited participants with a stenosis ≥50%, although ACST-1 had no fixed minimum cut- off. All these trials reported significant benefit in favour of CEA. Although there are no direct RCTs evaluating the safety and efficacy of CAS over medical therapy, three RCTs compared the safety and efficacy of CAS with CEA, namely Stenting and angioplasty with protection in patients at high risk for endarterectomy (SAPPHIRE), Carotid revascularisation endarterectomy versus stenting trial (CREST-1) and Asymptomatic carotid trial 1 (ACT-1) trials.[5,6,16] [Table 4] None of the three studies showed a difference in event rates between CEA and CAS, providing evidence that carotid artery stenting with embolic protection is a reasonable alternative to endarterectomy in patients at average risk for CEA. However, the major limitation across all surgical trials in ACS is that the best medical management was not well established. Although aggressive medical treatment in ACAS trial constituted only aspirin[17], current concept of aggressive medical treatment includes lipid lowering therapy[18,19] and optimal medical management of comorbidities like diabetes mellitus[20,21], hypertension[22,23], modification of life style including smoking

Table 6: Cohort studies comparing carotid revascularisation versus medical therapy in patients with asymptomatic carotid stenosis

Trial (Year)	*n*	Follow-up	30-day stroke			Long-term stroke rate				*P*
			CEA	CAS	MT	Definition	CEA	CAS	MT	
Libman *et al*.[35] (1994)	215	Mean 3.8 Years	4.7%	-	0	Any stroke	13%	-	16%	N.S.
Lim *et al*.[36] (2019)	409	Mean 5 years	2.0%*	-	0.6%	Any ipsilateral stroke	5.6%*	-	5.5%	N.A.
Kang *et al*.[37] (2021)	1089	Median 2.3 years	0.98%	4.0%	0	Any Ipsilateral stroke	0.65%	3.68%	1.98%	<0.001
Keyhani *et al*.[38] (2020)	5221	Mean 5 years	2.5%†	-	N.A.	Any stroke	6.7%	-	6.2%	N.A.

N.S=Not specified, NA: Not available, MT: Medical treatment, CEA=Carotid endarterectomy, CAS=Carotid artery stenting. *CEA in combination with medical treatment, †stroke and death

Table 7: Clinical/imaging features associated with an increased risk of stroke in patients with ACS[41,42]

Imaging/clinical parameter	OR/HR (95% CI)
Spontaneous MES on TCD	7.46 (2.24-24.89)
Plaque echolucency on Duplex US	2.61 (1.47-4.63)
Spontaneous MES on TCD + uniformly or predominantly echolucent plaque (70-99% stenosis)	10.61 (2.98-37.82)
Stenosis progression (50-99% stenosis)	1.92 (1.14-3.25)
Severe stenosis (50-70%)	-
Silent infarction on CT (60-99% stenosis)	3.0 (1.46-6.29)
Impaired cerebrovascular reserve (70-99% stenosis)	6.14 (2.77-4.95)
Intraplaque haemorrhage on MRI	3.66 (2.77-4.95)
Contralateral stroke/TIA	3.0 (1.9-4.73)
Lipid rich necrotic core	1.5 (0.4-5.5)
Plaque ulceration	2.4 (0.4-13.2)
AHA lesion type 4, 5 or 6	28.7 (1.6-513.0)

MES=Microembolic signals; TCD=Transcranial doppler; OR=Odds Ratio, HR=Hazard Ratio, CI=Confidence Interval, US=Ultrasound, CT=Computed tomography, MRI=Magnetic resonance imaging, AHA=American Heart Association

cessation, moderation of alcohol intake, change in dietary habits and physical exercise[24-27] [Table 5].

In 1995, ACAS trial reported 5-year risk of "ipsilateral" stroke of 11.0% (2.2% per annum) in patients receiving medical treatment with aspirin.[3] By 2004, the 5-year risk in ACST was reduced to 5.3% (1.1% per annum), whereas in years 6 to 10, the risk of "ipsilateral stroke" has decreased further to 3.6% (0.7% per annum) with modern medical treatment.[4] Evolution of medical treatment in the last two decades, especially with the introduction of intensive lipid lowering therapy has revolutionised the management of these patients.[18,29,30] A meta-analysis of the three most recently published studies on ACS patients receiving the best medical treatment showed an annual risk of 0.49% which is even less compared to the annual risk recorded in the 6-10 years results of ACST-1 trial.[31] These results signify that RCTs done so far have not included the best medical treatment. To support this notion, use of lipid lowering therapy and antihypertensive drugs increased significantly towards the end of study period in ACST-1 trial.[4] In the OxVasc study, the risk of ipsilateral stroke was only 0.34% per year in ACS patients receiving contemporary medical therapy.[32] Spence *et al*.[33] showed that intensive medical therapy based on treating arteries instead of treating risk factors was associated with lower risk of stroke and myocardial infarction (MI).

So had the medical treatment been optimal in the earlier RCTs, the results might have been different. There have been claims that advances in technology and increased experience may have led to reduction in risks following CAS and CEA which may increase the benefit of intervention in these patients. Naylor *et al*.[34] reanalysed the 5 and 10-years data from the ACAS and ACST trial with an assumption of 0% procedural risk. Modelling for a 0% procedural risk meant that more than 90% of these procedures were still unnecessary. On the contrary, in some cohort studies that included all three treatment groups, the results are conflicting [Table 6]. All these factors highlight the need for studies that can evaluate the efficacy of optimal medical management in comparison with CEA and CAS.

Risk Stratification

Offering routine carotid revascularisation to every patient with asymptomatic carotid artery stenosis is no longer considered as the optimal management. Equally suboptimal, however, is the policy of offering only best medical treatment to these patients and not considering any of them for revascularisation. Some patients may not respond to medical management, and they may benefit from carotid revascularisation. It is essential to identify these subsets of patients who are at high risk of recurrence of events. Degree of stenosis alone may not be the best approach for identification of these patients. In the last few years, several methods have been proposed as reliable predictors for the identification of patients at high risk of stroke.[39] For some of these predictors, the evidence is adequate and robust, whereas for others it is weaker. Micro embolic signals detected on transcranial Doppler is a simple, convenient and cost-effective method that can help in risk stratification of these patients.[40]

Table 7 summarises the clinical and imaging features that are associated with increased risk of stroke/TIA in ACS patients.[41]

Need for Future Trials

Although there are trials supporting revascularisation and emerging evidence towards best medical therapy, there is a lack of consensus as reflected in the guidelines addressing the management of these patients. Though guidelines recommend

Table 8: Summarised characteristics of the on-going RCTs in patients with ACS

Study	Design	Eligibility	Primary outcome	Estimated enrollment	Estimated completion (month/year)
CREST-2[44]	2 two-arm trials CAS + OMT vs OMT CEA + OMT vs OMT	>70% ACS (NASCET)	Stroke and death within 44 days of randomisation and ipsilateral stroke thereafter up to 4 years	2480	December 2022
ECST-2[45]	OMT vs OMT + revascularisation (CEA or CAS, prespecified before randomisation)	>50% SCS/ACS (NASCET)	Any stroke at any time, plus non- stroke death occurring within 30 days of revascularisation	2000	March 2022
ACST-2[46]	CEA vs CAS	ACS patients with uncertainty of treatment with CEA/CAS	Peri-procedural risks (within 30 days) of CEA or CAS and long-term (5-year) prevention of stroke and of disabling or fatal stroke	3600	2021

CREST-2: Carotid Revascularisation Endarterectomy versus Stenting Trial 2; ECST-2:European Carotid Surgery Trial 2 ACST-2: Asymptomatic Carotid Surgery Trial; CAS: Carotid artery stenting; CEA: Carotid endarterectomy; OMT: Optimal medical treatment; ACS: Asymptomatic carotid stenosis; SCS: Symptomatic carotid stenosis; NASCET: North American Symptomatic Carotid Endarterectomy Trial

CEA in management of ACS patients, the data is based on trials that appear to be of only historical importance. However, intervention in every patient with ACS is not worthwhile. AHA recognises that only highly selected patients should undergo carotid revascularisation but have not defined what is highly selected population.[13] Risk stratification through various methods has been proposed for identifying the high risk population but there are no studies to suggest that selective screening will reduce fatal or disabling strokes. Finally, the recent decline in stroke rates with optimal medical management has not been evaluated in an RCT. It is difficult to frame guidelines for management of these patients with the existing controversies. With the recent publication of studies suggesting an association between ACS and cognitive decline the clinical decision-making is going to become worse.[43] Hence there is a need for trials which can clear the existing controversies. CREST-2,[44] ECST-2,[45] and ACST-2[46] are some of the ongoing RCTs in patients with ACS. Table 8 provides characteristics of these ongoing trials. The results of these trials should answer the role of optimal medical treatment, indications for revascularisation (CEA/CAS) and risk stratification of patients with ACS. In the meantime, patients referred for revascularisation should have evidence of vulnerable plaque.

Conclusion

Asymptomatic carotid stenosis is a risk factor for stroke, myocardial infarction and mortality. Improvements in medical therapy have reduced the risk of cerebrovascular events possibly below a threshold where carotid revascularisation would still benefit the average risk patient. Although the results of the ongoing trials CREST-2,[44] ECST-2,[45] and ACST-2[46] awaited, all patients with ACS should receive optimal medical management for control of risk factors and comorbidities and patients with vulnerable plaque should be considered for revascularisation.

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